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**Neuroergonomics Deep Dive Literature Review, Volume 2:
Neuroergonomics and Performance: Prediction, Assessment, and
Facilitation**

**Victor Chan, James Christensen, Nicholas DelRaso, Gregory Funke, Benjamin Knott,
April Rose Panganiban, Clayton Stanley, Krystal Thomas**

Air Force Research Laboratory

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14. ABSTRACT This report is the second of two volumes summarizing published papers that were reviewed broadly within the area of neuroergonomics, with a specific focus on Air Force interests. The included references are not intended to be exhaustive, but rather to include review articles and representative empirical papers by the key researchers in each topic, thus providing a solid basis for understanding the state of this research.					
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Neuroergonomics Deep Dive Literature Review, Volume 2:

Neuroergonomics and Performance: Prediction, Assessment, and Facilitation

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Chapter 1

Introduction

This report is the second volume of the two-volume literature report stemming from the Human Effectiveness Directorate Neuroergonomics Deep Dive. An overview of the purpose and scope of this report may be found in Volume 1; Volume 2 summarizes the six remaining topical areas in Neuroergonomics.

The first area to be reviewed in this report is research on the genetics of human performance. This is a difficult and potentially controversial area of research, as it can create complex ethical issues regarding individual rights. Beyond the individual, the results of genetic studies could have implications affecting family members or even entire ethnic groups. Nevertheless, the contribution of genetic factors to human performance in numerous areas of Air Force interest renders it of significant importance. A better understanding of the genetic underpinnings of performance could enable not only discovery of particular innate talents, but also optimization of training regimens and/or working environments to maximize the genetic potential of each individual. Additionally, accurate and reliable performance prediction could be enabled by better understanding of the interaction between genetic and environmental factors. Work of this type is decidedly neuroergonomic; as discussed in Volume 1, neuroscience funding for genetic research is largely focused on genetic disorders and genetic markers associated with increased risks or early onset of pathological states, rather than normal work function. This has created an opportunity for AFRL to be a leader in this area.

Proteomic and metabolomic assessment of cognition is the second area. The assessment of protein expression and metabolite concentrations offers a novel means to fill in a key intermediate step in the pathway from genetic underpinnings to day-to-day human performance. Advancements in assessment techniques may offer the possibility of noninvasive measurement, enabling these techniques to contribute to a broad understanding of cognitive state, necessary for applying cognitive state monitoring technology in Air Force domains. Many of the comments made regarding genetics apply here; what research has been done to date is focused on pathology, leaving healthy humans a key niche for AFRL.

The third area to be reviewed is biologically-informed cognitive modeling. Cognitive modeling has undergone rapid advancement in recent years, as researchers have sought to build increasingly elaborate computational models of human cognition. Such models have several potential Air Force applications, offering the potential for performance prediction in both the short and long term. In the short term, models could predict performance impairments before they occur, and in the long term they could aid in predicting the efficacy and optimal scheduling of training. However, the majority of this work is still based on performance measures such as response time and accuracy; very little work has been done to date to connect neurophysiological state to model predictions. Cognitive models in the context of neuroergonomics present mutually beneficial possibilities, with models aiding in the prediction and interpretation of neurophysiological data, while such data can inform, update, and constrain the model.

Adaptive interfaces are the fourth area to be reviewed, in particular adaptive interfaces based on neuroergonomic monitoring techniques. This research is focused on applying these monitoring techniques to create adaptive systems that are aware of and responsive to human

cognitive state. It therefore entails not only the collection and analysis of neurophysiological data, but also linking that analysis to system responses that maintain or improve performance. Many Air Force operations could benefit from such technology; current research has demonstrated applicability to the simultaneous control of multiple remotely-piloted aircraft though Air Force operators of many types could be aided in this way. AFRL has a history and reputation for doing quality work in this particular area that renders it uniquely capable of continuing to make significant contributions.

The fifth area to be reviewed is adaptive training. While performance-based adaptive training techniques are well-known and actively studied, neurophysiologically-driven adaptation is a very new area of research, with some theoretical speculation published but essentially no empirical data or proof of concept. The hope is that neurophysiology could provide continuous feedback on learner state, even in training scenarios where performance is difficult or impossible to assess automatically. This feedback could then be used to modify scenario scheduling or difficulty to maintain an optimal learning state - analogous to what a one-on-one human instructor would do. Decreased training time and increased effectiveness are the expected results. This type of system may be particularly well-suited to complex operational tasks of the type performed by the Air Force.

Neuroergonomics in a teaming context is the last area to be reviewed. Air Force operations increasingly require teams to be rapidly formed, with members often distributed around the world; this has created unique challenges that could be addressed with this type of research. By using neuroergonomic assessment techniques, teams may be assembled of individuals with complementary cognitive skills; by monitoring team members and providing that information to either the team or to supervisors, some of the benefits of face-to-face interaction may be provided with minimal bandwidth required. This area, similar to the previous, is very novel with essentially no published empirical studies. By leveraging previous work in performance-based team facilitation, AFRL can rapidly become a leader in this area.

To reiterate the conclusion of Volume 1, it is important to stress that this literature review is not intended to be exhaustive; rather, it is intended to provide an annotated bibliography that covers the overall state-of-the-art in each of these research areas, and in so doing place AFRL research within the context of the larger research community. Neuroergonomics has the potential to enable incredible capabilities of significant interest to the Air Force, encompassing a full range of techniques and analysis from the molecular level to groups of individuals working together; realizing this potential will require sustained focus and investment in this work.

Chapter 2

Performance Genetics

This section contains a total of 42 articles covering the genetics/genetic analysis of three related aspects of human performance, namely cognitive performance, physical performance and fatigue-related conditions. As performance is the outcome of the interaction between multiple subsystems in humans, it is perhaps not surprising that certain genes and/or genetic polymorphisms are involved in more than one aspect of human performance. However, it should be noted that articles related to the conceptual theories and technical details of genetics were kept to a minimum, as these might not be relevant information to those who are not working in this field. Another feature of this collection is that almost all studies employed the approach of genome-wide association scan/study (GWAS). Although the candidate gene approach might still have some utilities under some special situations, the general consensus in this field is that GWAS is at least several orders of magnitude more powerful, especially for studying complex polygenic traits. While this collection is not an exhaustive list of articles in these areas, it does capture the most significant scientific findings in the PubMed Database. Finally, as the majority of biomedical/biological research is supported by National Institutes of Health with a mission of promoting health and human diseases intervention, a number of articles, especially in the areas of cognitive performance and fatigue-related conditions, thus have varying degrees of medical research connections. However, it should be emphasized that this has also been kept to a minimum, due to the sensitivity of this issue.

Cognitive Performance

1. **Wright, M.J., Luciano, M., Hansell, N.K., Geffen, G.M., Geffen, L.B., Martin, N.G. (2002). Genetic sources of covariation among P3(00) and online performance variables in a delayed-response working memory task. *Biological Psychology*, 61(1-2), 183-202.**

The authors found an association between of frontal P3 latency and task performance, with genes accounting for a large part of the covariation (>70%). However, genes influencing P3 amplitude mediated only a small part (2%) of the total genetic variation in task performance. While task performance mediated 15% of the total genetic variation in IQ, there was no association between P3 latency and IQ or P3 amplitude with IQ. These results suggest genes act on specific sub-components of various cognitive processes.

2. **Wright M., De Geus, E., Ando, J., Luciano, M., Posthuma, D., Ono, Y., Hansell, N., ...Boomsma, D. (2001). Genetics of cognition: outline of a collaborative twin study. *Twin Research*, 4 (1), 48-56.**

The authors found that heritability of Full Scale IQ was 87% in the Netherlands, 83% in Australia, and 71% in Japan. Heritability for processing speed and working memory indices ranged from 33-64%. The associations of IQ with reaction time and inspection time replicated previous findings with those of higher cognitive ability showing faster speed of processing. There are significant correlations between IQ and the spatial span working memory task (storage and executive processing) and the delayed response working memory task, with those of higher cognitive ability showing better memory performance.

3. **Butcher, L.M., Davis, O.S., Craig, I.W., & Plomin, R. (2008). Genome-wide quantitative trait locus association scan of general cognitive ability using pooled DNA and 500K single nucleotide polymorphism microarrays. *Genes, Brain and Behavior*, 7 (4), 435-46.**

Multivariate quantitative genetic analyses have shown that the same set of genes affects diverse cognitive abilities as well as learning disabilities. In this autosomal genome-wide association scan of general cognitive ability (g), >500,000 SNPs were screened in a sample of >7000 7-year-old children. Although six SNPs yielded significant associations across the normal distribution of g, none of these SNPs accounted for more than 0.4% of the variance of g. The authors thus concluded that QTL effect sizes, even for highly heritable traits such as cognitive abilities and disabilities, are much smaller than previously assumed.

4. **Huentelman, M.J., Papassotiropoulos, A., Craig, D.W., Hoernndli, F.J., Pearson, J.V., Huynh, K.D., Corneveaux, J., ... Stephan, D.A. (2007). Calmodulin-binding transcription activator 1 (CAMTA1) alleles predispose human episodic memory performance. *Human Molecular Genetics*, 16 (12), 1469-77.**

The authors conducted a genome-wide screen at >500 000 SNPs for the performance on an episodic recall memory test. SNPs within the calmodulin-binding transcription activator 1 (CAMTA1) gene were significantly associated with memory performance. A follow up study, focused on the CAMTA1 locus in an independent cohort consisting of cognitively normal young adults, singled out the SNP rs4908449 as the most significant SNP in the region (p=0.0002). The CAMTA1 locus encodes a transcription factor that interfaces with the calcium-calmodulin system of the cell to alter gene expression patterns. A functional magnetic resonance imaging experiment on individuals matched for memory performance identified CAMTA1 allele-specific upregulation of medial temporal lobe brain activity in those individuals harboring the 'at-risk' allele for poorer memory performance.

5. **Knafo, A., Israel, S., Darvasi, A., Bachner-Melman, R., Uzefovsky, F., Cohen, L., Feldman, E., ... Epstein, R.P. (2008). Individual differences in allocation of funds in the dictator game associated with length of the arginine vasopressin 1a receptor RS3 promoter region and correlation between RS3 length and hippocampal mRNA. *Genes Brain and Behavior*, 7 (3), 266-75.**

The authors hypothesized that human altruistic behavior is to some extent hardwired. A likely candidate that may contribute to individual differences in altruistic behavior is the arginine vasopressin 1a (AVPR1a) receptor. Participants (of the Dictator Game for real money payoffs) with short versions (308-325 bp) of the AVPR1a RS3 repeat allocated significantly fewer shekels to the 'other' than participants with long versions (327-343 bp). This gene, contributing to social bonding in lower animals, also appears to operate similarly in human behavior. This result strongly suggests a common evolutionary mechanisms and shows that a common human polymorphism contributes to decision making in an economic game.

6. **Papassotiropoulos A, Stephan DA, Huentelman MJ, Hoerndli FJ, Craig DW, Pearson JV, Huynh KD, Brunner F, ...DeQuervain, D.J. (2006). Common Kibra alleles are associated with human memory performance. *Science*, 314 (5798), 75-8.**

The authors found that the genomic locus encoding the brain protein KIBRA was significantly associated with memory performance in three independent, cognitively normal cohorts from Switzerland and the United States. Gene expression studies showed that KIBRA was expressed in memory-related brain regions, and functional magnetic resonance imaging detected KIBRA allele-dependent differences in hippocampal activations during memory retrieval. These results strongly suggest a role for KIBRA in human memory.

7. **Morley KI, & Montgomery GW. (2001). The genetics of cognitive processes: candidate genes in humans and animals. *Behavioral Genetics*, 31 (6), 511-31.**

It is widely believed that numerous genes contribute to individual variation in human cognition. An extensive literature search compiles a list of over 150 candidate genes that likely influence some aspect of cognition. This survey confirms that many genes are associated with cognitive variation and highlights the complexity of the genetic architecture of human cognition.

8. **Savitz, J., Solms, M., & Ramesar, R. (2006). The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes, Brain and Behavior*, 5 (4), 311-28.**

The important contribution of genetic factors to the development of cognition and intelligence is widely acknowledged. However, identification of these genes has proven to be difficult. A large body of evidence implicates the prefrontal cortex and its dopaminergic circuits in cognition. The genetic association studies on polymorphisms of catechol-O-methyltransferase (COMT) and the dopamine receptor genes, D1, D2 and D4 were reviewed.

Additionally, the evidence implicating brain-derived neurotrophic factor (BDNF) in neuropsychological function was also evaluated. Both the COMT val158met and the BDNF val66met polymorphisms appear to influence cognitive function, but the specific neurocognitive processes involved continue to be a matter of debate. The complexity of the relevant molecular pathways makes the inference of simple causal relationships difficult.

9. **Kravitz, H.M., Meyer, P.M., Seeman, T.E., Greendale, G.A., & Sowers, M.R. (2006). Cognitive functioning and sex steroid hormone gene polymorphisms in women at midlife. *American Journal of Medicine*, 119 (9 Suppl 1), S94-S102.**

The authors examined the frequencies of specific SNPs to determine whether variation in 6 estrogen-related genes was associated with differences in cognitive functioning in women at midlife. Three genes involved in estrogen synthesis and metabolism (e.g. estrogen receptor 1, hydroxysteroid (17-beta) dehydrogenase 2 and cytochrome P450, family 19, subfamily A, polypeptide 1) are associated with performance differences on cognitive function tests, including the Digit Span Backward Test (a measure of working memory), the Symbol Digit Modalities Test (a measure of perceptual speed), and the East Boston Memory Test (a measure of episodic memory). However, the effects of these estrogen-related polymorphisms on cognitive functions vary by race/ethnicity.

- 10. Wilkening, S., Chen, B., Bermejo, J.L., & Canzian, F. (2009). Is there still a need for candidate gene approaches in the era of genome-wide association studies? *Genomics*, 93 (5), 415-9.**

Most genetic variants associated with complex traits in humans are believed to have a small effect size. As genome-wide association techniques are feasible, the authors assessed the coverage of all currently known genes and biological processes in different populations by commercially available microarrays. They found that the coverage of individual genes and pathways by current commercial genotyping platforms is satisfactory for the vast majority of RefSeq gene regions. However, depending on the gene or the population, there may be situations under which candidate gene approaches, especially when looking at polymorphisms with low allele frequencies, could be useful.

- 11. Williams, R., Lim, J.E., Harr, B., Wing, C., Walters, R., Distler, M.G., Teschke, M., ...Palmer, A.A. (2009). A common and unstable copy number variant is associated with differences in Glo1 expression and anxiety-like behavior. *PLoS One*, 4 (3), e4649.**

Glyoxalase 1(Glo1) has been implicated in anxiety-like behavior in animal models and in multiple psychiatric diseases in humans. The authors evaluated copy number variants among inbred mouse strains and identified a duplication of approximately 475 kb tandem on chromosome 17 that includes Glo1. Associations were detected between multiple duplication-containing haplotypes, Glo1 expression and anxiety-like behavior in both inbred strain panels and outbred CD-1 mice.

- 12. Cirulli, E.T., Kasperavičiūtė, D., Attix, D.K., Need, A.C., Ge, D., Gibson, G., Goldstein, D.B. (2010). Common genetic variation and performance on standardized cognitive tests. *European Journal of Human Genetics*. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20125193>.**

Recent genome-wide association studies showed that common genetic variation in individually detectable polymorphisms has limited impact on many human traits. One explanation for this observation is that many of these traits are genetically heterogeneous. This leads to the idea that relevant endophenotypes (e.g. aspects of cognition) could be more genetically tractable. The authors conducted a genome-wide association study with two tests of executive function (Digit Symbol and Stroop Color-Word) in 1086 healthy volunteers and they found that no single common variant has a large effect (i.e. that can explain >4-8% of the population variation) on the performance of healthy individuals on standardized cognitive tests.

- 13. Donohoe, G., Walters, J., Morrism D.W., Quinn, E.M., Judge, R., Norton, N., Giegling, I., ...Corvin, A. (2009). Influence of NOS1 on verbal intelligence and working memory in both patients with schizophrenia and healthy control subjects. *Archives of General Psychiatry*, 66 (10), 1045-54.**

Neuronal nitric oxide synthase 1 (NOS1) has been implicated in both cognition and schizophrenia susceptibility in human and animal studies. The authors investigated if the SNP

(rs6490121), associated with a potential risk of schizophrenia, has any influence on cognition (e.g. IQ, episodic memory, working memory, and attentional control) in healthy control subjects and in patients with schizophrenia and they found that a main effect of NOS1 genotype on verbal IQ and working memory in the Irish sample where the homozygous carriers of the schizophrenia risk G allele performed poorly compared with the other genotype groups. This result was replicated in the German samples with the GG genotype carriers performing below other genotype groups. The German samples revealed that NOS1 GG carriers also underperformed on additional IQ measures (full-scale and performance IQ).

14. Need, A.C., Attix, D.K., McEvoy, J.M., Cirulli, E.T., Linney, K.L., Hunt, P., Ge, D., ...Goldstein, D.B. (2009). A genome-wide study of common SNPs and CNVs in cognitive performance in the CANTAB. *Human Molecular Genetics*, 18 (23), 4650-61.

These authors performed a genome-wide association study involving 11 cognitive phenotypes from the Cambridge Neuropsychological Test Automated Battery. They were unable to find any genome-wide significant associations with either SNPs or common copy number variants. These authors also investigated SNPs that have harbored rare variants associated with neuropsychiatric disorders and found that only neurexin 1 (NRXN1) showed evidence of significant association with cognition. These results might suggest that common genetic variation does not strongly influence cognition in healthy subjects.

15. Potkin, S.G., Turner, J.A., Guffanti, G., Lakatos, A., Torri, F., Keator, D.B., & Macciardi, F. (2009). Genome-wide strategies for discovering genetic influences on cognition and cognitive disorders: methodological considerations. *Cognitive Neuropsychiatry*, 14 (4-5), 391-418.

These authors reviewed strategies for the identification of common genetic variation that modulate normal and abnormal cognition. Evidence suggests that the use of a quantitative phenotype in combination with a GWAS might provide some advantages over a case-control design. Using this approach, putative susceptibility genes for schizophrenia, which affect prefrontal efficiency and have important roles in cell migration, forebrain development and stress response, were identified. This result demonstrated that the use of QT as phenotypes provide increased statistical power over categorical association approaches.

16. Hashimoto, R., Noguchi, H., Hori, H., Ohi, K., Yasuda, Y., Takeda, M., & Kunugi, H. (2009). Association between the dysbindin gene (DTNBP1) and cognitive functions in Japanese subjects. *Psychiatry Clinical Neuroscience*, 63 (4), 550-6.

The dystrobrevin binding protein 1 (DTNBP1), which has an influence on influencing cognitive performance, is a susceptibility gene for schizophrenia. These authors investigated a possible association between a SNP of DTNBP1 (rs2619539) and memory and IQ in 70 schizophrenia patients and 165 healthy volunteers in a Japanese population. They found that this SNP was associated with two memory scales on the Wechsler Memory Scale-Revised (verbal memory and general memory) and three subcategories of the Wechsler Adult Intelligence Scale-Revised (vocabulary, similarities and picture completion) in healthy subjects. The authors thus

concluded that a risk-independent SNP in DTNBP1 may have an impact on cognitive functions such as memory and IQ in healthy subjects.

- 17. Deary, I.J., Johnson, W., & Houlihan, L.M. (2009). Genetic foundations of human intelligence. *Human Genetics*, 126 (1), 215-32.**

Individual differences in intelligence (cognitive abilities) are a prominent aspect of human psychology, and play a substantial role in influencing important life outcomes. Approximately half of the variance in a broad range of cognitive abilities is accounted by a general cognitive factor (g). Small proportions of cognitive variance are caused by separable broad domains of mental function. The substantial remainder is caused by variance that is unique to highly specific cognitive skills. The heritability of g is substantial - it increases from a low value in early childhood of about 30%, to well over 50% in adulthood, which continues into old age.

- 18. Asher, J.E., Lamb, J.A., Brocklebank, D., Cazier, J.B., Maestrini, E., Addis, L., Sen, M., ...Monaco, A.P. (2009). A whole-genome scan and fine-mapping linkage study of auditory-visual synesthesia reveals evidence of linkage to chromosomes 2q24, 5q33, 6p12, and 12p12. *American Journal of Human Genetics*, 84 (2), 279-85.**

Synesthesia is characterized by anomalous sensory perception and associated alterations in cognitive function due to interference from synesthetic percepts. Initial familiarity studies show evidence of a strong genetic predisposition with a single-gene X-linked dominant mode of inheritance. Subsequent analyses in larger samples indicated that the mode of inheritance was likely to be more complex. These authors thus conducted a whole-genome linkage scan for auditory-visual synesthesia. Significant linkage at the genome-wide level was detected to chromosome 2q24. This result suggests that auditory-visual synesthesia is likely to be an oligogenic disorder subjected to multiple modes of inheritance and locus heterogeneity.

- 19. Schaper, K., Kolsch, H., Popp, J., Wagner, M., & Jessen, F. (2008). KIBRA gene variants are associated with episodic memory in healthy elderly. *Neurobiology of Aging*, 29 (7), 1123-5.**

Previous genome wide association study on cognition revealed the association of a SNP of the KIBRA gene with episodic memory in healthy young and middle aged volunteers. These authors reported an independent replication study on a sample of healthy elderly subjects and they found that the effect sizes of the respective KIBRA SNP on memory even exceed those of the initial report. However, the effect is restricted to hippocampus-related episodic memory without effects on frontal lobe function.

- 20. Luciano, M., Wright, M.J., Duffy, D.L., Wainwright, M.A., Zhu, G., Evans, D.M., & Geffen, G.M., et al. (2006). Genome-wide scan of IQ finds significant linkage to a quantitative trait locus on 2q. *Behavioral Genetics*, 36 (1), 45-55.**

The authors conducted a genome-wide linkage scan on tasks highly predictive of IQ (Multidimensional Aptitude Battery subtests and verbal, performance and full scale scores, WAIS-R Digit Symbol subtest, Schonell Graded Word Reading Test, and Cambridge Contextual

Reading Test). They also identified significant linkage for the Cambridge reading test and performance IQ to the same region on chromosome 2, with respective LOD scores of 4.15 and 3.68.

- 21. Reinvang, I., Lundervold, A.J., Wehling, E., Rootwelt, H., & Espeseth, T. (2010). Epistasis between APOE and nicotinic receptor gene CHRNA4 in age related cognitive function and decline. *Journal of the International Neuropsychological Society*, 16(3):424-32.**

The authors conducted genetic analysis of apolipoprotein E (APOE) and Cholinergic Receptor for Nicotine Alpha 4 (CHRNA4). Relatively stronger effects of APOE on memory and of CHRNA4 on speeded tasks were observed. Interactive effects of APOE and CHRNA4 in several cognitive domains were also observed that carrier of APOE epsilon4/CHRNA4 TT was associated with slower and less efficient performance, and with steeper decline in speed tasks and in delayed recall.

- 22. Reinvang, I., Winjevoll, I.L., Rootwelt, H., & Espeseth, T. (2010) Working memory deficits in healthy APOE epsilon 4 carriers. *Neuropsychologica*, 48(2):566-73.**

The authors found that in an aged group of healthy individuals (mean age = 64.5 years) reduced working memory performance was associated with APOE epsilon4 genotype, with sex and epsilon4 dose as modifying variables.

- 23. Reinvang, I., Lundervold, A.J., Rootwelt, H., Wehling, E., & Espeseth, T. (2009) Individual variation in a cholinergic receptor gene modulates attention. *Neuroscience Letters*, 453(3):131-4.**

Polymorphism in the CHRNA4 gene (rs1044396) are associated with aspects of visual and auditory attentional processing. These authors reported that TT homozygotes perform speed and attention tasks more slowly than TC or CC allele carriers, with stronger effects on complex attention tasks. There are however no parallel effects on memory function. The results suggested that reduction in nicotinic receptor efficiency affects attention and speed, but not memory.

- 24. Espeseth, T., Rootwelt, H., & Reinvang, I. (2009) Apolipoprotein E modulates auditory event-related potentials in healthy aging. *Neuroscience Letters*, 459(2):91-5.**

Individuals of APOE epsilon3 homozygotes, epsilon3/epsilon4 heterozygotes, or epsilon4 homozygotes underwent an auditory three-stimulus oddball task while their event-related potentials (ERPs) were recorded. It was found that heterozygotes had lower N1 amplitudes than the epsilon3 homozygotes, APOE genotype also significantly modulated N2 latency that epsilon4 homozygotes had longer N2 latencies.

Physical Performance

1. **Ahmetov, I.I., Rogozkin, V.A. (2009). Genes, athlete status and training -- An overview. *Medicine and Sports Science*, 54, 43-71.**

There is evidence suggesting genes have strong influences on human physical performance and elite athlete status. A literature search revealed that at least 36 genetic markers (located within 20 autosomal genes, mitochondrial DNA and Y-chromosome) are linked to elite athlete status. Thirty-nine genetic markers (located within 19 genes and mitochondrial DNA) may explain, in part, an interindividual variability of physical performance characteristics in response to endurance/strength training. These findings suggest these genetic markers might be used in an individually tailored prescription of lifestyle/exercise for health and sports performance.

2. **Spielmann, N., Leon, A.S., Rao, D.C., Rice, T., Skinner, J.S., Rankinen, T., & Bouchard, C. (2007). Genome-wide linkage scan for submaximal exercise heart rate in the HERITAGE family study. *Heart and Circulatory Physiology*, 293 (6), H3366-71.**

The purpose of this study was to identify regions of the human genome linked to submaximal exercise heart rates in the sedentary state and in response to a standardized 20-wk endurance training program in blacks and whites of the HERITAGE Family Study. Steady-state heart rates were measured at the relative intensity of 60% maximal oxygen uptake (HR60) and at the absolute intensity of 50 W (HR50). The most promising regions for fine mapping in the HERITAGE Family Study were found on 2q33 for HR50 training response in whites, on 10q25-26 for baseline HR60 in blacks, and on 18q21-22 for both baseline HR50 and training response (posttraining minus baseline) HR60 in whites.

3. **Rankinen, T., Argyropoulos, G., Rice, T., Rao, D.C., & Bouchard, C. (2010). CREB1 Is a Strong Genetic Predictor of the Variation in Exercise Heart Rate Response to Regular Exercise: The HERITAGE Family Study. *Circulation and Cardiovascular Genetics*. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20407090>**

The authors conducted a genome-wide linkage scan and identified a quantitative trait locus (QTL) for exercise training-induced changes in submaximal exercise (50W) heart rate (DeltaHR50) on chromosome 2q33.3-q34 in the HERITAGE Family Study. Two SNPs, rs2253206 and rs2360969, located in the 5' region of the cAMP responsive element binding protein 1 (CREB1) gene show the strongest association with DeltaHR50. Regression modeling of the 39 most significant SNPs identified nine SNPs that collectively explained 20% of the DeltaHR50 variance in the single-SNP analyses. CREB1 SNP rs2253206 had the strongest effect (5.45% of variance), followed by SNPs in the FASTKD2 (3.1%), MAP2 (2.6%), SPAG16 (2.1%), ERBB4 (3 SNPs ~1.4% each), IKZF2 (1.4%), and PARD3B (1.0%) loci. Functional studies revealed that the common allele of rs2253206 exhibits significantly ($p < 0.05$) lower promoter activity than the minor allele.

4. **Bray, M.S., Hagberg, J.M., Pérusse, L., Rankinen, T., Roth, S.M., Wolfarth, B., & Bouchard, C. (2009). The human gene map for performance and health-related fitness phenotypes: the 2006-2007 update. *Medical Science in Sports Exercise*, 41 (1), 35-73.**

This article provides an update of the human gene map for physical performance and health-related fitness phenotypes. The fitness and performance map now includes 214 autosomal gene entries and quantitative trait loci plus seven others on the X chromosome. There are also 18 mitochondrial genes that have been shown to influence fitness and performance phenotypes.

- 5. Yang, N., Garton, F., & North, K. (2009). Alpha-actinin-3 and performance. *Medicine in Sports Science*, 54, 88-101.**

The human alpha-actinin-3 (ACTN3) is a major structural component of the Z line in skeletal muscle, and its expression is restricted to the fast glycolytic fibers that are responsible for forceful contraction at high velocity. There is a common stop codon polymorphism R577X in the ACTN3 gene, and homozygosity for the R577X null-allele results in the absence of alpha-actinin-3 in fast muscle fibers. In the general population, the ACTN3 genotype contributes to the normal variations in muscle strength and sprinting speed. The ACTN3 R577X genotype influences athletic performance that the frequency of the XX genotype in sprint athletes is significantly lower than that of controls. In an animal model of ACTN3 deficiency, slower contractile properties, decreased muscle mass and fiber diameter are observed, while oxidative enzyme activity and fatigue resistance are increased suggesting a more efficient oxidative metabolism phenotype.

- 6. Eisenach, J.H., Barnes, S.A., Pike, T.L., Sokolnicki, L.A., Masuki, S., Dietz, N.M., Rehfeldt, K.H., ...Joyner, M.J. (2005). Arg16/Gly beta2-adrenergic receptor polymorphism alters the cardiac output response to isometric exercise. *Journal of Applied Physiology*, 99 (5), 1776-81.**

Normotensive adults homozygous for glycine (Gly) of the Arg16/Gly beta2-adrenergic-receptor polymorphism have greater forearm beta2-receptor mediated vasodilation and a higher heart rate (HR) response to isometric handgrip than arginine (Arg) homozygotes. The authors thus measured continuous HR, arterial pressure, and cardiac output during isometric, 40% submaximal handgrip to fatigue in healthy subjects homozygous for Gly and Arg. Handgrip produced similar increases in arterial pressure and venous norepinephrine and epinephrine concentrations. However, HR increased more in the Gly group, and this caused cardiac output to be higher. This result thus suggests that Gly16 homozygotes generate a higher cardiac output to maintain the pressor response to handgrip.

- 7. Von Känel, R., Maly, F.E., Frey, K., Fischer, J.E. (2003). Contribution of the type 1 plasminogen activator inhibitor 4G/5G gene polymorphism to impaired fibrinolysis in vital exhaustion. *Italian Heart Journal*, 4 (11), 791-6.**

Inappropriate coping with chronic stress may result in a state of "vital exhaustion". This could be mediated by impaired fibrinolysis due to an increase in type 1 plasminogen activator inhibitor (PAI-1). These authors investigated the contribution of the PAI-1 4G/5G gene polymorphism to the plasma levels of PAI-1 in exhaustion. Across all subjects, exhausted individuals had higher PAI-1 antigen levels than non-exhausted subjects. No significant difference was observed in the PAI-1 antigen levels between exhausted and non-exhausted individuals with both the 4G/4G and the 4G/5G polymorphisms. With the 5G/5G

polymorphism, exhausted subjects however had higher PAI-1 antigen levels than non-exhausted subjects, suggesting that exhausted subjects might have less fibrinolytic capacity than non-exhausted subjects.

- 8. Echegaray, M., & Rivera, M.A. (2001). Role of creatine kinase isoenzymes on muscular and cardiorespiratory endurance: genetic and molecular evidence. *Sports Medicine*, 31 (13), 919-34.**

The ability to perform well in activities that require muscular and cardiorespiratory endurance is a trait significantly influenced by the genetic make-up of individuals. Creatine kinase (CK) and phosphocreatine (PCr) form an important metabolic system for buffering large variations in energy demand. CK-M is the predominant form in both skeletal and cardiac muscle, while CK-B is expressed to a greater extent in heart than in skeletal muscle. The abundance and activity of the CK-MB dimer increase in response to cardiorespiratory endurance training. CK-M knocked-out mice showed significant increases in fatigue resistance together with increased aerobic capacity. Human studies of CK-M gene sequence variations have a significant association between cardiorespiratory endurance as indexed by maximal oxygen uptake following 20 weeks of training.

- 9. Eisenach, J.H., McGuire, A.M., Schwingler, R.M., Turner, S.T., & Joyner, M.J. (2004). The Arg16/Gly beta2-adrenergic receptor polymorphism is associated with altered cardiovascular responses to isometric exercise. *Physiological Genomics*, 16 (3), 323-8.**

A polymorphism in the gene encoding the beta(2)-adrenergic receptor (Arg16Gly) is associated with altered vasodilator responses to beta(2)-agonists, which may modulate the pressor response to endogenous catecholamines during stress. The authors thus measured mean arterial pressure (MAP) and heart rate (HR) during mental stress (MS), cold pressor test (CPT), and handgrip (HG) to fatigue in healthy subjects homozygous for Gly16 or Arg16. For MS and CPT, MAP and HR did not differ between genotype groups. Handgrip also produced similar increases in MAP. However, the change in HR during HG was greater in the Gly16 homozygotes than that in Arg16 homozygotes. The authors thus concluded that the greater HR response to exercise in the Gly16 homozygotes may serve to maintain the pressor response (increased cardiac output).

Fatigue Susceptibility

- 1. Dahlqvist, J., Orlén, H., Matsson, H., Dahl, N., Lönnerholm, T., & Gustavson, K.H. (2009). Multiple epiphyseal dysplasia. *Acta Orthop*, 80 (6), 711-5.**

Multiple epiphyseal dysplasia (MED) is a genetically and clinically heterogeneous skeletal dysplasia characterized by early-onset osteoarthritis. The progression of the disease also affects muscles, with increasing atrophy, resulting in muscle fatigue and pain. The authors identified an exon 3 donor splice mutation in the COL9A2 gene in all 17 affected family members in a 6-generation MED family.

2. **Carlo-Stella, N., Bozzini, S., De Silvestri, A., Sbarsi, I., Pizzochero, C., Lorusso, L., Martinetti, M., ...Cuccia, M. (2009). Molecular study of receptor for advanced glycation endproduct gene promoter and identification of specific HLA haplotypes possibly involved in chronic fatigue syndrome. *International Journal of Immunopathological Pharmacology*, 22 (3), 745-54.**

Chronic fatigue syndrome (CFS) is a long-lasting fatigue that compromises at least 50% of a subject's daily activities without other known cause. Immune dysfunction has been implicated in the etiology of CFS. These authors studied the receptor for advanced glycation end product (RAGE) polymorphisms and HLA-DRB1 alleles in CFS patients and matched controls, and the result suggests that HLA haplotypes rather than single alleles of RAGE or of DRB1 genes seem to be involved in CFS.

3. **Ortega-Hernandez, O.D., Cuccia, M., Bozzini, S., Bassi, N., Moscovitch, S., Diaz-Gallo, L.M., Blank, M., ...Shoenfeld, Y. (2009). Autoantibodies, polymorphisms in the serotonin pathway, and human leukocyte antigen class II alleles in chronic fatigue syndrome: are they associated with age at onset and specific symptoms? *Annals New York Academy of Science*, 1173, 589-99.**

The authors evaluated the influence of polymorphisms in the serotonin pathway, and human leukocyte antigen (HLA) class II genes on age at chronic fatigue syndrome (CFS) onset and symptoms. Polymorphisms in the promoter of the serotonin transporter gene (l/s) and a SNP in the serotonin receptor-2A gene (A/G) as well as HLA class II alleles were studied. They found that an age at CFS onset (ACFSO) during the third decade of life was associated with the serotonin receptor AA genotype and the HLA-DRB1*03 allele. An ACFSO during the fourth decade of life was associated with the HLA-DRB1*07 allele. An ACFSO > 43 years was associated with having at least one copy of the serotonin G allele. The serotonin AG genotype however was protective against depressive symptoms.

4. **Light, A.R., White, A.T., Huguen, R.W., & Light, K.C. (2009) Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. *Journal of Pain*, 10 (10), 1099-112.**

Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue, often accompanied by widespread muscle pain. Previous studies implicated dysregulation of the sympathetic nervous system (SNS), and immune system (IS) in CFS. Acid sensing ion channel (ASIC3), purinergic type 2X receptors (P2X4 and P2X5) and the transient receptor potential vanilloid type 1 (TRPV1) are molecular receptors in sensory neurons detecting metabolites that cause acute muscle pain and possibly muscle fatigue. CFS patients, who had lower expression of beta-2 adrenergic receptors, showed no other differences from 16 control subjects before exercise. After a sustained moderate exercise test, CFS patients showed greater increases than control subjects in the metabolite detecting receptors (ASIC3, P2X4, and P2X5), for SNS receptors (alpha-2A, beta-1, beta-2, and COMT) and IS genes (IL10 and TLR4). These increases were highly correlated with symptoms of physical fatigue, mental fatigue, and pain. These findings thus strongly suggest dysregulation of metabolite detecting receptors as well as SNS and IS in CFS.

5. **Aouizerat, B.E., Dodd, M., Lee, K., West, C., Paul, S.M., Cooper, B.A., Wara, W., ...Miaskowski, C. (2009). Preliminary evidence of a genetic association between tumor necrosis factor alpha and the severity of sleep disturbance and morning fatigue. *Biological Research for Nursing, 11* (1), 27-41.**

Although fatigue and sleep disturbance are prevalent symptoms in oncology patients and their family caregivers, little is known about the factors that contribute to interindividual variability in symptom severity. These authors investigated the association of a functional genetic variation in tumor necrosis factor-alpha (TNF α 308G>A [rs1800629] promoter polymorphism) with overall sleep disturbance and fatigue. The result showed that common allele homozygotes had higher levels of sleep disturbance and morning fatigue than minor allele carriers.

6. **Buss, C., Schuelter, U., Hesse, J., Moser, D., Phillips, D.I., Hellhammer, D., & Meyer, J. (2007). Haploinsufficiency of the SERPINA6 gene is associated with severe muscle fatigue: A de novo mutation in corticosteroid-binding globulin deficiency. *Journal of Neural Transmitters, 114* (5), 563-9.**

Corticosteroid-binding globulin (SERPINA6) deficiency is characterized by reduced plasma corticosteroid-binding capacity. Low basal cortisol levels are associated with hypo-/hypertension and muscle fatigue. A patient with severe muscle fatigue, normal blood pressure, and abnormal high saliva cortisol levels following a standardized stress test, was found heterozygous for a de novo 367 asparagine-encoding variant of the corticosteroid-binding globulin gene. This is the first case of de novo mutation reported for corticosteroid-binding globulin deficiency and implicates a pathogenic role of variants of SERPINA6 in some cases of muscle fatigue.

7. **Smith, J., Fritz, E.L., Kerr, J.R., Cleare, A.J., Wessely, S., & Matthey, D.L. (2005). Association of chronic fatigue syndrome with human leucocyte antigen class II alleles. *Journal of Clinical Pathology, 58* (8), 860-3.**

A possible association between human leucocyte antigen (HLA) class II antigens and chronic fatigue immune dysfunction has been shown in some, but not all, studies. These authors found that an increased frequency of HLA-DQA1*01 and HLA-DQB1*06 alleles in patients with CFS. However, only the association between HLA-DQA1*01 and CFS was significant in logistic regression models. Thus, CFS appears to be associated with HLA-DQA1*01.

8. **Torpy, D.J., Bachmann, A.W., Gartside, M., Grice, J.E., Harris, J.M., Clifton, P., Eastel, S., ...Whitworth, J.A. (2004). Association between chronic fatigue syndrome and the corticosteroid-binding globulin gene ALA SER224 polymorphism. *Endocrine Research, 30* (3), 417-29.**

Chronic fatigue syndrome (CFS) is characterized by idiopathic fatigue with postexertional exacerbation. Previous studies indicate a substantial genetic etiologic component to CFS. Severe corticosteroid-binding globulin (CBG) gene mutations have been associated with CFS.

The authors found that there is a trend toward a preponderance of serine224 homozygosity in CBG among the CFS patients. CBG levels were higher in Serine/Alanine (Ser/Ala) than Ala/Ala subjects and higher again in Ser/Ser subjects. Homozygosity for the serine allele of the CBG gene may predispose to CFS, perhaps due to altered CBG-cortisol transport function or immune-cortisol interactions.

9. Narita, M., Nishigami, N., Narita, N., Yamaguti, K., Okado, N., Watanabe, Y., & Kuratsune, H. (2003). Association between serotonin transporter gene polymorphism and chronic fatigue syndrome. *Biochemical and Biophysical Research Communications*, 311 (2), 264-6.

Interaction between the hypothalamo-pituitary-adrenal axis and the serotonergic system is thought to be disrupted in chronic fatigue syndrome (CFS) patients. The authors investigated a serotonin transporter (5-HTT) gene promoter polymorphism, which affects the transcriptional efficiency of 5-HTT, in CFS patients. They subsequently found that the longer (L and XL) allelic variants is significantly higher in CFS patients, compared to the controls. Thus, attenuated concentration of extracellular serotonin due to longer variants may be the cause of higher susceptibility to CFS.

Key Researchers

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Chapter 3

Proteomic and Metabolomic Characterization of Cognition

This section contains a total of 41 articles concerned with proteomic and metabolomic biomolecular characterization of cognitive performance. The biomolecular characterization of protein profiles (proteomics) and metabolite profiles (metabonomics) in human biofluids (i.e. cerebral spinal fluid, blood, urine, etc.) may identify early cognitive decrement prior to impacting warfighter mission performance. None of the literature references cited below were found to be concerned with only proteomic or metabolomic characterization of cognitive function. In all cases, cited references of biomolecular characterization of cognition (i.e. learning, memory, vigilance, etc) were associated with a study of a particular disease state. A majority of the cited articles involving proteomic or metabolomic characterization of cognition were associated with Alzheimer disease. Other disease states included diabetes, alcohol and cocaine addiction, schizophrenia and various other neurodegenerative disease states. The brief summary of selected papers describes proteomic and metabolomic techniques used to investigate cognitive performance during these neurodegenerative disease states ranging from mild to severe cognitive impairment. Referenced material includes both animal and human studies.

Proteomics

1. **Britschgi, M. & Wyss-Coray, T. (2009). Blood Protein Signature for the Early Diagnosis of Alzheimer Disease. *Archives of Neurology*, 66 (2), 161-165.**

Paper describes proteomic approach using a blood-based panel of secreted proteins that distinguish between control and people with Alzheimer's disease (AD). The same proteins also predicted progression to AD in preclinical patients with mild cognitive impairment several years before clinical diagnosis for AD was made.

2. **Sköld, K., Svensson, M., Normann, M., Sjögren, B., Svenningsson, P., & Andrén, P. (2007). The significance of biochemical and molecular sample integrity in brain proteomics and peptidomics: Stathmin 2-20 and peptides as sample quality indicators. *Proteomics*, 7, 4445–4456.**

Methods paper describing a novel method for preventing degradation of proteins and peptides in postmortem tissue using rapid and uniform conductive heat transfer on tissue prior to the actual sample preparation procedures, which enables the relatively low-abundant neuropeptides to remain intact, minimizes degradation of proteins by proteolysis, and conserves the post-translational modifications of the neuropeptides.

3. **Roche, S., Gabelle, A., & Lehmann, S. (2008). Clinical proteomics of the cerebrospinal fluid: Towards the discovery of new biomarkers. *Proteomics Clinical Applications*, 2, 428–436.**

Few cerebral spinal fluid (CSF) proteomic studies have been performed in comparison to those on blood. This review paper provides a proteomics description of the CSF, summarizes the current clinical use of this fluid and describes CSF clinical proteomics examination.

4. **Zetterberg, H., R  tschi, U., Portelius, E., Brinkmalm, G., Andreasson, U., Blennow, K., & Brinkmalm, A. (2008). Clinical proteomics in neurodegenerative disorders. *Acta Neurologica Scandinavica*, 118, 1–11.**

This review paper provided an update on recent advances in clinical neuroproteomics, a biomarker discovery field that has expanded immensely during the last decade, and gives an overview of the most commonly used techniques and the major clinically relevant findings these techniques have lead to.

5. **Freeman, W.M., VanGuilder, H.D., Bennett, C., & Sonntag, W.E. (2009). Cognitive performance and age-related changes in the hippocampal proteome. *Neuroscience*, 159 (1), 183–195.**

This paper described proteomic changes that suggest that age-related alterations act synergistically with other perturbations to result in cognitive decline. This study also demonstrated the importance of examining behaviorally-defined animals in proteomic studies, as comparison of young to old animals regardless of behavioral performance would have failed to detect many cognitive impairment-specific protein expression changes evident when behavioral stratification data was used.

6. **Hu, Y., Malone, J.P., Fagan, A.M., Townsend, R.R., & Holtzman, D.M. (2005). Comparative Proteomic Analysis of Intra- and Inter-individual Variation in Human Cerebrospinal Fluid. *Molecular & Cellular Proteomics*, 4, 2000–2009.**

Among six study subjects, the paper described comparison between four cognitively normal and two very mildly demented subjects that yielded some proteins that have been identified in previous Alzheimer's biomarker studies. The results of the study also validated their method of identifying differences in proteomic profiles of cerebral spinal fluid (CSF) samples and have important implications for the design of CSF biomarker studies for Alzheimer's and other central nervous system disorders.

7. **Simonsen, A.H., McGuire, J., Hansson, O., Zetterberg, H., Podust, V.N., Davies, H.A., Waldemar, G.,... Blennow, K. (2007). Novel Panel of Cerebrospinal Fluid Biomarkers for the Prediction of Progression to Alzheimer Dementia in Patients with Mild Cognitive Impairment. *Archives of Neurology*, 64, 366-370.**

Proteomic profiling of cerebrospinal fluid provided a novel panel of 17 potential biomarkers for prediction of mild cognitive impairment progression to Alzheimer's. Five of the identified biomarkers were relevant to the pathogenesis of Alzheimer's and may help elucidate the molecular pathways in which they may function.

8. Kobeissy, F.H., Sadasivan, S., Oli, M.W., Robinson, G., Larner, S.F., Zhang, Z., Hayes, R.Y., & Wang, K.K.W. (2008). **Neuroproteomics and systems biology-based discovery of protein biomarkers for traumatic brain injury and clinical validation.** *Proteomics Clinical Applications*, 2, 1467–1483.

Review paper that evaluated the current status of traumatic brain injury biomarker discovery using neuroproteomics techniques, and at what stage they are at in their clinical validation. In addition, the paper discusses the need for strengthening the role of systems biology and its application to the field of neuroproteomics due to its integral role in establishing a comprehensive understanding of specific brain disorder and brain function in general.

9. Song, F., Poljak, A., Smythe, G.A., & Sachdev, P. (2009). **Plasma biomarkers for mild cognitive impairment and Alzheimer's disease.** *Brain Research Reviews*, 61, 69-80.

Paper reviews the current state of knowledge on plasma biomarkers for mild cognitive impairment (MCI) and Alzheimer's disease (AD), including unbiased proteomics and recent longitudinal studies. Paper discusses panel of 18 biomarkers reported for MCI and AD and concludes findings need replication in longitudinal studies.

10. Sunyer, B., Diao, W., & Lubec, G. (2008). **The role of post-translational modifications for learning and memory formation.** *Electrophoresis*, 29, 2593–2602.

Review paper discusses role of post-translational modifications (PTMs) in the cognitive processes of learning and memory. Paper also discusses technologies that allow reliable detection and quantification of PTMs of proteins involved in the cognitive system that will contribute to the understanding of mechanisms for learning and memory formation at the chemical level.

11. Anderson, C.N.G & Grant, S.G.N. (2006). **High throughput protein expression screening in the nervous system – needs and limitations.** *Journal of Physiology*, 575 (2), 367–372.

Proteomic studies of the synapse have revealed that the postsynaptic density is the most complex multiprotein structure yet identified, with ~103 different proteins. Paper reviews existing large-scale protein expression studies and the specific technical obstacles that need to be overcome before applying the scaling used in nucleic acid based approaches.

12. Martins-de-Souza, D., Gattaz, W.F., Schmitt, A., Rewerts, C., Maccarrone, G., Dias-Neto, E., & Turck, C.W. (2009). **Prefrontal cortex shotgun proteome analysis reveals altered calcium homeostasis and immune system imbalance in schizophrenia.** *European Archives of Psychiatry and Clinical Neurosciences*, 259, 151–163.

Paper describes global proteomic analysis of post-mortem dorsolateral prefrontal cortex samples from schizophrenia patients and non-schizophrenic individuals that were performed using stable isotope labeling and shotgun proteomics. In addition, paper identified a number of

new potential markers that may contribute to the understanding of the pathogenesis of this complex disease.

- 13. Caudle, W.M., Pan, S., Shi, M., Quinn, T., Hoekstra, J., Beyer, R.P., Montine, T.J., ... Zhang, J. (2008). Proteomic identification of proteins in the human brain: Towards a more comprehensive understanding of neurodegenerative disease. *Proteomics Clinical Applications*, 2, 1484–1497.**

Review article focused on the recent progress related to identification of proteins in the human brain under normal as well as pathological conditions, mainly Alzheimer and Parkinson disease, their potential application in biomarker discovery, and discusses the current advances in protein identification aimed at providing a more comprehensive understanding of the brain.

- 14. Ward, M., Guntert, A., Campbell, J., & Pike, I. (2009). Proteomics for Brain Disorders—The Promise for Biomarkers. *Biomarkers in Brain Disease: Annals New York Academy of Science*, 1180, 68–74.**

Article reviews the issues discussed during the proteomics breakout sessions held at the Biomarkers for Brain Disorders conference in Oxford in January 2009. Authors point out that although there are very few qualified biomarkers that have arisen as a result of proteomics efforts to date, that to be successful in the development of biomarkers for brain disorders will require multidisciplinary teams and continued collaboration between academia, the biotechnology industry, and the pharmaceutical sector.

- 15. Tannu, N.S. & Hemby .SE. (2006). Methods for proteomics in neuroscience. *Progress in Brain Research*, 158, Hemby & Bahn (Eds.), Elsevier B.V.**

Review article examines the subcellular organelle isolation, protein fractionation and separation of proteins, and the methods for quantifying relative gene product expression between samples. An overview of the techniques used currently to assign post-translational modification status on a proteomics scale and the feasible coverage of the proteome, ability to detect unique cell components such as post-synaptic densities and membrane proteins, resource requirements and quantitative as well as qualitative reliability of different approaches are also discussed.

- 16. Xi, L., Junjian, Z., Yumin, L., Yunwen, L., & Hongbin, W. (2009). Serum biomarkers of vascular cognitive impairment evaluated by bead-based proteomic technology. *Neuroscience Letters*, 463, 6–11.**

Paper investigated biomarkers of vascular cognitive impairment (VCI) in humans (n = 30). Twenty-four peptides were significantly differently expressed between VCI patients and controls. There were seven peptides selected for a diagnostic model that demonstrated a sensitivity of an internal and external validation of 95% and 80% respectively, while demonstrating a specificity of 100% for both. A fragment of the trace-amine associated receptor 6 (TAAR6) protein was identified as a potential clinical biomarker for the screening and diagnosis of VCI.

- 17. Opii, W.O., Joshi, G., Head, E., Milgram, N.W., Muggenburg, B.A., Klein, J.B., Pierce, W.M., ...Butterfield, D.A. (2008). Proteomic identification of brain proteins in the canine model of human aging following a long-term treatment with antioxidants and a program of behavioral enrichment: Relevance to Alzheimer's disease. *Neurobiology of Aging*, 29, 51–70.**

Study authors hypothesized a possible mechanism for the improvement of cognition in aged treated animals mediated through the protection of neuronal function as a consequence of reduced oxidative damage and improved antioxidant reserves and potential increase in expression of key brain proteins associated with neuronal improvement. Paper reports that the use of antioxidants composed of mitochondrial cofactors and cellular antioxidants and a program of behavioral enrichment could potentially protect proteins from oxidative damage and enhance mitochondrial function leading to observed improved memory and cognitive function.

- 18. Jung, S.M., Lee, K., Lee, J.W., Namkoong, H., Kim, H.K., Kim, S., Na, H.R., ...Kim, J.W. (2008). Both plasma retinol-binding protein and haptoglobin precursor allele 1 in CSF: Candidate biomarkers for the progression of normal to mild cognitive impairment to Alzheimer's disease. *Neuroscience Letters*, 436, 153–157.**

Paper discusses applied proteomics approaches to investigate candidate cerebral spinal fluid (CSF) biological markers in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Paper reports findings that suggested that the CSF levels of both plasma retinol-binding protein and haptoglobin precursor allele 1 may be candidate biomarkers for the progression of normal to MCI to AD.

- 19. Zheng, J.F., Patil, S.S., Chen, W.Q., An, W., He, J.Q., Höger, H., & Lubec, G. (2009). Hippocampal Protein Levels Related to Spatial Memory Are Different in the Barnes Maze and in the Multiple T-Maze. *Journal of Proteome Research*, 8, 4479–4486.**

Study investigated the hypothesis that differences in cognitive performances of mice in two land mazes would be accompanied by differences in hippocampal protein levels. Levels of hippocampal proteins associated with spatial memory from several pathways including signaling, chaperone, and metabolic cascades were found to be significantly different between two spatial memory tasks in mice.

- 20. Castegna, A., Thongboonkerd, V., Klein, J.B., Lynn, B., Markesbery, W.R., & Butterfield, D.A. (2003). Proteomic identification of nitrated proteins in Alzheimer's disease brain. *Journal of Neurochemistry*, 85, 1394–1401.**

Increased levels of nitrated proteins have been reported in Alzheimer's disease (AD) brain and cerebral spinal fluid, demonstrating the potential involvement of reactive nitrogen species (RNS) in neurodegeneration associated with this disease. Present study identified six targets of protein nitration in AD brain that provided support for the importance of oxidative stress in the progression of this dementing disease and potentially established a link between RNS-related protein modification and neurodegeneration.

- 21. Thouvenot, E., Urbach, S., Dantec, C., Poncet, J., Séveno, M., Demettre, E., Jouin, P., ...Marin, P. (2008). Enhanced Detection of CNS Cell Secretome in Plasma Protein-Depleted Cerebrospinal Fluid. *Journal of Proteome Research*, 7, 4409–4421.**

Methods paper adapted the most complete multiaffinity depletion method available to remove 20 abundant plasma proteins from a cerebral spinal fluid (CSF) pool originating from patients with various cognitive disorders. Removal of these 20 major plasma proteins from CSF was found to improve detection of brain cell-derived proteins in CSF and may facilitate identification of relevant biomarkers in CSF proteome profiling analyses.

- 22. Thambisetty, M., Hye, A., Foy, C., Daly, E., Glover, A., Cooper, A., Simmons, A., ...Lovestone, L. (2008). Proteome-based identification of plasma proteins associated with hippocampal metabolism in early Alzheimer's disease. *Journal of Neurology*, 255, 1712–1720.**

The aim of this study was to identify plasma proteins associated with known *in vivo* markers of Alzheimer's disease (AD) activity and to test them for their association with progression of AD measured by MRS neuro-imaging. The association of plasma complement factor-H (CFH) and alpha-2-macroglobulin (A2M) with hippocampal N-acetylaspartate/myo-inositol ratio (NAA/mI) suggested that these proteins may reflect disease progression in early AD.

- 23. Sultana, R. Perluigi, M., Newman, S.F., Pierce, W.M., Cini, C., Coccia, R., & Butterfield, D.A. (2010). Redox Proteomic Analysis of Carbonylated Brain Proteins in Mild Cognitive Impairment and Early Alzheimer's Disease. *Antioxidants and Redox Signaling*, 12, 327–336.**

Study used a parallel proteomic approach to identify oxidatively modified proteins in the inferior parietal lobule (IPL) from human subjects with mild cognitive impairment (MCI) and early stage-Alzheimers disease (EAD). Results implied that some of the common targets of protein carbonylation correlated with Alzheimer's neuropathology and suggested a possible involvement of protein modifications in the progression of this disease.

- 24. Butterfield, D.A., & Sultana, R. (2006). Redox proteomics identification of oxidatively modified hippocampal proteins in mild cognitive impairment: Insights into the development of Alzheimer's disease. *Neurobiology of Disease*, 22, 223 – 232.**

Using redox proteomics, study determined that protein oxidation was significantly increased in the hippocampi of mild cognitive impaired (MCI) subjects, and that these oxidatively modified proteins were identified as A-enolase (ENO1), glutamine synthetase (GLUL), pyruvate kinase M2 (PKM2) and peptidyl-prolyl cis/trans isomerase 1 (PIN1). Study concluded that protein oxidation played a significant role in the development of Alzheimer's disease (AD) from MCI and that the oxidative inactivation of ENO1, GLUL, PKM2 and PIN1 was involved in the progression of AD from MCI.

- 25. Mueller, C., Zhou, W., Vanmeter, A., Heiby, M., Magaki, S., Ross, M.M., Espina, V., ... Kirsch, W.M. (2010). The heme degradation pathway is a promising serum**

biomarker source for the early detection of Alzheimer's disease. *Journal of Alzheimer's Disease*, 19 (3), 1081-91.

Study involved collection of serial serum samples from cognitively normal, mild cognitively impaired (MCI), and mild Alzheimer's disease (AD) participants, and using mass spectrometry they identified several promising leads for biomarker development, such as prosaposin, phospholipase D1, biliverdin reductase B, and S100 calcium binding protein A7. Study findings strongly implicated the heme degradation pathway as a promising source of protein biomarkers for the early detection of AD.

26. Schneider, G. & Cirelli, C. (2005). Identification of molecular inhibitors of cognitive performance: a large-scale proteomic analysis in sleep deprived flies, rats and sparrows. (Accession Number: ADB314372).

Phase I SBIR study to use Proteinchip© Arrays with Surface-Enhanced-Laser-Desorption/Ionization Time-of-Flight Mass Spectrometry to obtain a large-scale profiling of the proteins whose brain expression is affected by sleep loss. ProteinChip© Arrays have been developed and marketed by Ciphergen Biosystems Inc., the “small business” in this proposal. The study was conducted in fruit flies, rats and migratory sparrows, and sleep recordings and sleep deprivation experiments were performed in the laboratory of Dr. Chiara Cirelli (University of Wisconsin – Madison)

Metabolomics

1. Hampel, H., Bürger, K., Teipel, S.J., Bokde, A.L.W., Zetterberg, H., & Blennow, K. (2008). Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. *Alzheimer's & Dementia*, 4, 38–48.

Paper is a survey of recent research, focusing on core biomarker candidates in Alzheimer's disease (AD). A number of neuroimaging candidate markers were found to be promising, such as hippocampus and entorhinal cortex volumes, basal forebrain nuclei, cortical thickness, deformation-based and voxel-based morphometry, structural and effective connectivity by using diffusion tensor imaging, tractography, and functional magnetic resonance imaging.

2. Greensberg, N., Grassano, A., Thambisetty, M., Lovestone, S., & Legido-Quigley, C. (2009). A proposed metabolic strategy for monitoring disease progression in Alzheimer's disease. *Electrophoresis*, 30, 1235–1239.

The paper described metabolomic statistical analysis on plasma fingerprints to investigate novel biomarkers indicative of Alzheimer's disease (AD), to consider the role of bile acids as AD biomarkers and to consider whether mild cognitive impairment (MCI) is a separate disease from AD. The findings of the study suggested that further investigation into the lipid fraction of the metabolome may yield useful biomarkers for AD and metabolomic profiles could be used to predict disease state in a clinical setting.

3. **Kaddurah-Daouk, R. & Krishnan, K.R.R. (2009). Metabolomics: A Global Biochemical Approach to the Study of Central Nervous System Diseases. *Neuropsychopharmacology Reviews*, 34, 173–186.**

This review article focused on applications of metabolomics for the study of diseases of the nervous system. Authors discussed concepts in metabolomics, tools used in metabolic profiling and early findings from the study of neuropsychiatric diseases, and drugs used to treat these diseases. Authors concluded that metabolomics is emerging as another powerful tool in central nervous system research.

4. **Zhang, X., Liu, H., Wu, J., Zhang, X., Liu, M., & Wang, Y. (2009). Metabonomic alterations in hippocampus, temporal and prefrontal cortex with age in rats. *Neurochemistry International*, 54, 481–487.**

Paper described “magic angle spinning” NMR technique for assessment of metabolic changes occurring in the hippocampus, temporal and prefrontal cortex of aged rats. Age-related metabolic changes were indicated and the study highlights the potential of metabolic profiling to enhance the understanding of biological mechanisms of brain aging.

5. **Meuller, S.G., Schuff, N., & Weiner, M.W. (2006). Evaluation of treatment effects in Alzheimer’s and other neurodegenerative diseases by MRI and MRS. *NMR in Biomedicine*, 19, 655–668.**

Currently, clinical outcome measures are used to assess the efficacy of neurodegenerative disease treatments. However, most clinical outcome measures have a low test–retest reliability and thus considerable measurement variance. Paper describes potential use of MRI/MRS to monitor objectively treatment effects in clinical trials of neurodegenerative diseases.

6. **Kantarci, K. (2007). ¹H Magnetic resonance spectroscopy in dementia. *The British Journal of Radiology*, 80, S146–S152.**

Paper reviews over a decade of MR spectroscopy literature in common dementias in order to demonstrate the potential clinical applications of the technique and its limitations in this field. ¹H magnetic resonance spectroscopy is unique among diagnostic imaging modalities because the signals from several different metabolites are measured within a single examination period.

7. **Brambilla, P., Stanley, J.A., Sassi, R.B., Nicoletti, M.A., Mallinger, A.G., Keshavan, M.S., & Soares, J.C. (2004). ¹H MRS Study of Dorsolateral Prefrontal Cortex in Healthy Individuals before and after Lithium Administration. *Neuropsychopharmacology*, 29, 1918–1924.**

Paper investigated the effects of lithium on N-acetyl-aspartate (NAA) levels in a sample of healthy individuals using in vivo ¹H MRS in dorsolateral prefrontal cortex (DLPFC), a region likely implicated in the pathophysiology of bipolar disorder. Contrary to prior MRS reports in

bipolar patients, study found that lithium administration did not significantly increase NAA levels in the DLPFC of healthy individuals.

- 8. Mason, G.F. & Krystal, J.H. (2006). MR spectroscopy: its potential role for drug development for the treatment of psychiatric diseases. *NMR in Biomedicine*, 19, 690–701.**

Paper reviews an array of the information that MRS offers about neurochemistry in general and psychiatric disorders and their treatment in particular, provides growing evidence of glial abnormalities in neuropsychiatric disorders and discuss what MRS is contributing to that line of investigation, and discusses where MRS techniques are headed and how those new techniques can contribute to studies of mechanisms of psychiatric disease and drug discovery.

- 9. Modrego, P.J., Fayed, N., & Pina, M.A. (2005). Conversion from Mild Cognitive Impairment to Probable Alzheimer's Disease Predicted by Brain Magnetic Resonance Spectroscopy. *American Journal of Psychiatry*, 162, 667–675.**

Objective of study was to determine whether findings from magnetic resonance spectroscopy (MRS) of the hippocampus and other cortical areas would predict conversion from amnesic mild cognitive impairment to probable Alzheimer's disease. MRS of the brain performed on patients with mild cognitive impairment was found to be a valuable tool in predicting conversion to probable Alzheimer's disease (occipital values were more reliable than hippocampal values in this prediction).

- 10. Dunne, V.G., Bhattachayya, S., Besser, M., Rae, C., & Griffin, J.L. (2005). Metabolites from cerebrospinal fluid in aneurysmal subarachnoid haemorrhage correlate with vasospasm and clinical outcome: a pattern-recognition 1H NMR study. *NMR in Biomedicine*, 18, 24–33.**

In this study, the global high-concentration metabolite composition of CSF was correlated with patient outcome after subarachnoid haemorrhage (SAH) using multivariate statistics and proton NMR spectroscopy. Pattern recognition models of the NMR data predicted Glasgow Coma Score, Hunt and Hess SAH severity score and cognitive outcome scores. Metabolomic approach allowed the prediction of outcome as well as confirming the presence of aneurysmal SAH.

- 11. Tukiainen, T., Tynkkynen, T., Mäkinen, V.P., Jylänki, P., Kangas, A., Hokkanen, J., Vehtari, A., ...Ala-Korpela, M. (2008). A multi-metabolite analysis of serum by 1H NMR spectroscopy: Early systemic signs of Alzheimer's disease. *Biochemical and Biophysical Research Communications*, 375, 356–361.**

Paper investigates a three-molecular-window approach for 1H NMR spectroscopy of serum to obtain specific molecular data on lipoproteins, various low-molecular-weight metabolites, and individual lipid molecules together with their degree of (poly)(un)saturation. The results of the study underlined the association between mild cognitive impairment and the metabolic syndrome.

- 12. Mahdi, A.A., Annarao, S., Tripathi, S., Nawab, A., Mahdi, F., Hasan, M., Roy, R., & Khetrpal, C.L. (2008). Correlation of Age-Related Metabonomic Changes in ¹H NMR Serum and Urine Profiles of Rats with Cognitive Function. *The Open Magnetic Resonance Journal*, 1, 71-76.**

Paper investigated metabonomic changes in young and aged male rats using 'in vivo' behavioral and metabonomic assessment in serum and urine. The metabonomic evaluation of age related changes in serum and urine showed altered concentrations of many Krebs cycle intermediates in old rats that were associated with diminished mitochondrial functioning. On the basis of their results, it was suggested that the observed changes may be an early clinical indication of cognitive decline related to dementia.

- 13. Neville, H.J. & Linton, R.W. (2004). Acquisition of a Magnetic Resonance Imaging system for Research on the Neural Basis of Human Cognition. DTIC Accession # ADA427437.**

Establishment of an imaging center at the University of Oregon, with support from DoD, was associated with the Brain Biology and Machine Initiative to create a world-leading center linking genomic and proteomics to human cognitive neuroscience research. Installation of a 3-Tesla functional Magnetic Resonance Imaging instrument in the Lewis Center for Neuroimaging at the University of Oregon led to studies investigating neural networks related to attention, memory, perception and learning.

- 14. Weiner, M.W. (2005). Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illness. DTIC Accession Number: ADA443757.**

The primary goal of this project was to test the hypotheses that subjects with Gulf War Illness (GWI) have reduced N-acetyl aspartate (NAA) in the basal ganglia and pons, which are not accounted for by confounds such as PTSD, depression, or alcohol abuse. The preliminary spectral data suggested that there were generally no differences between groups in the bilateral basal ganglia or pons.

- 15. Pettegrew, J.W. (2009). Molecular/Metabolomics Biomarker of Autism. Accession Number: DA373725.**

Highly innovative neuromolecular biomarkers unique to both childhood (β -ATP, iPDE, iPME, and $(\alpha-\gamma)$ -ATP) and adolescent (PCr, Pi, iPDE, and $(\alpha-\gamma)$ -ATP) autism subjects were identified by non-invasive *in vivo* magnetic resonance spectroscopy in high-functioning autism subjects. The identified biomarkers not only provided new insights into the molecular basis for autism, but also provided a non-invasive method to guide the development and monitor clinical efficacy of therapeutic modalities.

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PROTEOMICS

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Chapter 4

Biologically-Informed Cognitive Modeling

Building a model requires developing a structure that enables the prediction of a variable of interest. This structure can take the form of a computer program which gets executed to generate predictions (computational cognitive modeling), a mathematical equation that maps a set of input states to output states (statistical modeling), a neural network (PDP modeling), or a structural diagram that predicts directions of certain trends (structural equation modeling). Most of the time, a model using a particular structure can be translated to the other structural forms (e.g., light can be thought of as both a wave and a particle, John Anderson has shown that ACT-R and Leabra are, broadly speaking, mutually coherent theories of the same unity of behavior). This means that the different modeling formalisms (i.e., the different approaches to specify a model) exist to describe our models on various planes of abstraction, so that we can better grasp what our models are actually saying about how our cognitive system works.

The cognitive constraints, much like the gravitational, electromagnetic, and quantum constraints for physics, actually tell the story about how our cognitive system works. These constraints – the mathematical equations embedded in the formalisms - are the pieces that actually predict behavior. Therefore, different modeling formalisms should not be thought of as opposing cognitive theories. Different theories lie on the plane of constraints, and not the plane of formalisms. For example, ACT-R has both a modeling formalism and a theory of cognition within it. The formalism is a lisp-based textual system to specify a computational cognitive model, and the theory is the underlying mathematical equations that constrain the system when the model is run. By swapping out one of the mathematical equations with another (i.e., switch constraints), or swapping out the lisp-based textual language used to specify the model (i.e., switch formalisms), can it still be called ACT-R? It is imperative not to confuse formalisms with constraints. The theory lies in the constraints, and not the formalism used to specify the constraints. In this way, biologically-informed cognitive modeling is a process of building a model for a task while testing, verifying, and discovering the biological constraints that both enable and limit our performance at the task.

1. **Howes, A., Lewis, R. L., & Vera, A. (2009). Rational adaptation under task and processing constraints: Implications for testing theories of cognition and action. *Psychological Review*, 116, 717-751.**

The authors assume that individuals adapt rationally to a utility function given constraints imposed by their cognitive architecture and the local task environment. Found strong fits of model to data using this paradigm. This allows the modeler to separate effects that were due to strategy, and effects that were due to architecture, which are confounded otherwise. This paper is pushing the cognitive modeling community away from fitting and more into exploring, which will require better tools and more computational resources to explore the space of the model and theory. Effects due to learning/training intersect with this methodology, because one can describe learning/training as the process of moving down the path of the strategy space, getting better and better utility function values, until the person is at the highest utility he/she can get (i.e., an expert). One could see using this modeling paradigm to model pilots switching tasks in the cockpit (and learning the optimal way to switch between tasks).

2. Raichle, M. E. (2006). The brain's dark energy. *Science*, 314, 1249-1250.

Looking at the DMN brain region, which acts as an 'uber-conductor to ensure that the cacophony of competing signals from one system do not interfere with those from another'. This article states that the brain 'continuously wrestles with the need to balance planned responses and the immediate needs of the moment'.

3. Rodgers, J. L. (2010). The epistemology of mathematical and statistical modeling: A quiet methodological revolution. *The American Psychologist*, 65, 1-12.

The author states that a quiet methodological revolution is occurring in psychology, where researchers are shifting away from the ridged null hypothesis significance testing, and moving more towards building models that accurately and simply describe reality.

4. Anderson, J., Bothell, D., Byrne, M., Douglass, S., Lebiere, C., & Qin, Y. (2004). An integrated theory of the mind. *Psychological Review*, 111, 1036–1060.

The authors describe the ACT-R theory of cognition, and present two experiments showing how the theory can be used to model tasks that require an integration and coordination between different perceptual/motor systems to do the task. Provided an overview of the general theory of ACT-R, and how each component maps back to biological processes and cortical regions. Links time that a module in ACT-R is active to generating a BOLD response, so that BOLD response patterns between model and data can be compared. This article also shows the general direction of ACT-R, which is an integrated theory of the mind informed by neuroscience.

5. Myers, C., Gray, W. D., Sims, C. R. (submitted). Soft constraints on visual search: Initial saccades are boundedly optimized to the cost-structure of the visual environment. *Journal of Vision*.

Built and tested a model of visual search that integrates both bottom-up (task independent) and top-down (task-dependent) salience. Used a Bayesian probabilistic model to account for how people find an optimal strategy to perform each experimental manipulation. Essentially, uses Bayes theorem to calculate the visual salience of objects displayed. Another 'rational analysis' approach to 'biologically inspired cognitive models'.

6. Lehman, J. F., Laird, J. E., & Rosenbloom, P. S. (1996). A gentle introduction to soar, an architecture for human cognition. In D. Scarborough & S. Sternberg (Eds.), *Invitation to Cognitive Science 4*: 211–253. Cambridge, MA: MIT Press.

The authors introduce Soar, which has a lot of general overlap with the ACT-R cognitive architecture. Uses symbolic and operator based manipulations, a goal state, learning & chunking, etc. It was found that Soar does differentiate between semantic and episodic memory components, which ACT-R does not do. ACT-R allows semantic memories to arise from repeated exposures to episodic memories. The article opens a research question of whether or

not there are different regions and components in the brain to support episodic & semantic memories.

7. **Kieras, D., & Meyer, D. E. (1997). An overview of the EPIC architecture for cognition and performance with application to human-computer interaction. *Human-Computer Interaction, 12*, 391–438.**

This article introduces EPIC, which has a lot of general overlap with both SOAR & ACT-R. However, EPIC does not assume a central bottleneck, so the 'executive control' can execute multiple tasks simultaneously. Sequential performance arises due to the sequential constraints on the perceptual and motor processes and not due to the central bottleneck directly.

8. **Lebiere, C., & Anderson, J. R. (1993). A connectionist implementation of the ACT–R production system. *Proceedings of the Fifteenth Annual Conference of the Cognitive Science Society*, 635–640. Mahwah, NJ: Lawrence Erlbaum Associates, Inc.**

The authors describe a method for implementing both the declarative memory retrieval mechanisms, as well as the goal/production structure of ACT-R as a connectionist neural network. Doing so constrains the type of productions that are possible, reducing the degrees of freedom that are usually available to the modeler when building productions. Shows that there's no reason a symbolic cognitive architecture can't be implemented as a PDP network.

9. **Plaut, D. C., & McClelland, J. L. (2010). Locating object knowledge in the brain: A critique of Bowers's (2009) attempt to revive the grandmother cell hypothesis. *Psychological Review, 117*, 284–290.**

Outlines the general PDP approach to cognitive modeling. "To us, it seems most important that the representations used in our models capture the same similarity structure that is captured by neural representations in the brain, and not that the individual neurons participating in these representations have individually interpretable (i.e., low perplexity) responses."

10. **Stocco, A., Lebiere, C., & Anderson, J. R. (2009). Dopamine, learning, and production rules: The basal ganglia and the flexible control of information transfer in the brain. In A. Samsonovich (Ed.) *Biologically Inspired Cognitive Architectures II*, 169–175. AAAI Press.**

Introduces a biological model of the basal ganglia, and shows how that model can be seen as a biological implementation of a production system. In short, the authors found the biological origins of 'Pavlov's Dog'.

11. **Mandal, S., Zhak, S., Sarpeshkar, R. (2009). A bio-inspired active radio-frequency silicon cochlea. *IEEE Journal of Solid-State Circuits, 44*, 1814–1828.**

The implant is built as an on-chip radio frequency (RF) spectrum analyzer that mimics the biological properties of the cochlea in the ear, but analyzes a much higher and broader frequency range than the ear does (600 MHz to 8 GHz). Reduces the power and complexity requirements

of the chip by two orders of magnitude when compared to using the standard Fast Fourier Transform chip design. Shows how research has evolved to do this spectrum analyzer computation extremely efficiently, and gives back to the community by showing how designers of hearing aids can make their products more effective.

12. Wilson, M. (2002). Six views of embodied cognition. *Psychonomic Bulletin & Review*, 9, 625–636.

Instead of arguing that the environment drives the mind, they argue that the mind can be used to manipulate the environment. Hunting/gathering/flight/fight is an example of the former, which is (presumably) a pretty basic human trait that is shared with many other species. However, verbal reasoning / imagining / algebraic manipulation / STM->LTM transferring are all examples of the latter argument that are traits fairly unique to humans. In short, this paper redefines the term 'embodied cognition' to put the mind back in control of the body, and not the other way around.

13. Myers, C., Gray, W. D. (2008). Visual scan adaptation during repeated visual search. *Journal of Vision*, 8 (6). doi: 10.1167/8.6.107

When trials were repeated in a simple search task, visual scan similarity and search efficiency increased. These increments in similarity and efficiency demonstrate the systematic and adaptive nature of visual scans to the characteristics of the visual environment during search.

14. Garonne, V., Stokes-Rees, I. & Tsaregorodsev, A. (2004). DIRAC: A scalable lightweight architecture for high throughput computing. In *Grid, 5th IEEE/ACM International Workshop on Grid Computing*. Pittsburgh, PA.

In the past 10 years, a combinatorially-explosive need for High Performance Computing to answer research questions in a reasonably quick timeframe has been seen. To make using HPC resources easier, many researchers have thought hard about how to abstract away the underlying details of the HPC system so that a user can easily leverage parallelized resources quickly to get work done. Grid computing is one of the ways to do this, where the aim is to have a single submission interface which pools the different types of HPC resources together (e.g., BOINC volunteer computing, supercomputing facilities, in-house clusters) and uses whatever is available to spread out the work. The aim with the MindModeling system at PALM is to do exactly this. To make a single model submission interface that's easy and intuitive, which abstracts away all the backend details about how exactly your model is getting parallelized and run on volunteer resources.

15. Banarjee, S., Grosan, C., Abraham, A. (2005). Modeling Crowd Behavior Using Emotional Ants. *Studia Universitatis Babes-Bolyai, Seria Informatica*, L(1).

This article models the movement of crowds in wartime situations using pheromones as a means of communicating the utility of different safe havens. Biologically inspired from how ants communicate information back and forth between colonies, and on trails moving from one colony to another.

- 16. Howes, A., Lewis, R. L., Vera, A. H., & Richardson, J. (2005). Information-requirements grammar: A theory of the structure of competence for interaction. In B. G. Bara & L. Barsalou & M. Bucciarelli (Eds.), *27th Annual Meeting of the Cognitive Science Society*, 595–600. Austin, TX: The Cognitive Science Society, Inc.**

The cognitive processing constraints that apply in general across all tasks, and then see how those constraints will interact to form behavior on the task at hand (i.e., the model). In this way, a particular model is any behavior that's possible under the given constraints. And the ideal model (and consequently, ideal behavior) is the model that behaves optimally under the current constraints. The 'path' to behaving optimally (shifting strategies) is now interesting, and this can be mapped to a form of a 'parameter search'.

- 17. Lewis, R.L., Howes, A., & Vera, A. H. (2004). A constraint-based approach to understanding the composition of skill. *Proceedings of the International Conference on Cognitive Modeling*, Pittsburgh, PA.**

A paper describing a method where the model for a task is generated automatically, based on the assumption that we are constrained cognitive processors and we try to string together subtasks in a manner that maximizes a utility function (e.g., minimize time on task) given our cognitive constraints. Uses the Prolog declarative programming language to specify constraints, and then search for 'cognitively-plausible' subtask orderings.

- 18. Walker, W., Lamere, P., Kwok, P., Raj, B., Singh, R., Gouvea, E., Wolf, P., and Woelfel, J. (2004). Sphinx-4: A flexible open source framework for speech recognition. (TR-2004-139). Sun Microsystems.**

Introduced sphinx-4, a modular and pluggable speech recognition system developed in Java. Different 'theories' of speech can be easily tested within the same sphinx-4 speech recognition framework. Sphinx is essentially a computational framework that allows you to easily specify your own modeling architecture (i.e., to swap out different theories). ACT-R is not like this, although ACT-UP (developed by Dr. Libiere) was developed towards this end. ACT-R's theory is a bit more entangled with the computational architecture, which makes the theory more difficult to modify.

- 19. Gonzalez, C., Lerch, J. F., & Lebiere, C. (2003). Instance-based learning in dynamic decision making. *Cognitive Science*, 27(4), 591–635.**

Introduced an instance-based model of learning, framed by the ACT-R cognitive architecture, and including a 'blending' component for retrieving the utility of past choices.

- 20. Ullman, M. T. (2001). A neurocognitive perspective on language: The declarative/procedural model. *Nature Reviews Neuroscience*, 2, 717–726.**

Presents a review of the neurological components of language; argues that the evidence favors a dual theory, which two separate declarative and procedural systems are competing against each other to decide on the correct conjugation of regular/irregular verbs.

- 21. Lee, M. D. (2008). Three case studies in the Bayesian analysis of cognitive models. *Psychonomic Bulletin & Review*, 15(1), 1–15.**

The authors talk about using Bayesian inference as a tool for analysis cognitive models. Uses three case studies (current cognitive models), and recasts them in a Bayesian framework. Bayesian analysis tools are pretty powerful and general. The paper also discusses how the same Bayesian analysis might be exactly what we're doing in our head when we analyze situations and make decisions. This is a form of biologically-inspired data analysis.

- 22. McEwen B.S. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiological Reviews*, 87, 873–904.**

This paper provided a substantial overview of all the different ways that stress can occur, and how it can interact with systems in the brain.

- 23. Ratcliff, R., Philiastides, M. G., & Sajda, P. (2009). Quality of evidence for perceptual decision making is indexed by trial-to-trial variability of the eeg. *Proceedings of the National Academy of Sciences*, 106, 6539-6544.**

This paper was based on the open question that, EEG data is strongly associated with 'drift rate', which is a metric (parameter) in the diffusion model. They found that EEG responses late in the trial were associated with drift rate, while earlier responses weren't. This data is a bit circular, but they're corroborating the diffusion model and saying that EEG observations late in the analysis can help set calibration values (i.e., the drift rate) for the model.

- 24. Ratcliff, R., & Rouder, J.N. (1998). Modeling response times for two-choice decisions. *Psychological Science*, 9, 347–356.**

Introduces a stochastic random-walk model that predicts the interplay between response time & accuracy on two-choice reaction tasks. Does not get into a neurological basis for the model in this paper; however, in previous work the authors find neurons that correlate with the drift rate parameter used in the model.

- 25. Douglass, S., & Myers, C. (submitted). Increasing the scale and performance of act-r's declarative memory with erlang. 10th International Conference on Cognitive Modeling.**

Provided an evaluation of a new modeling and simulation framework (based in the programming language Erlang) that incorporates ACT-R's declarative calculus for memory retrievals from hundreds of thousands of memories within extended finite state automata that provide the developer with the ability to model across many different timescales. Essentially

massively parallelized the spreading activation calculation in ACT-R, and extends the ways that this calculation can be done.

26. Jilk, D. J., Lebiere, C., O'Reilly, R. C., & Anderson, J. R. (2008). SAL: An explicitly pluralistic cognitive architecture. *Journal of Experimental and Theoretical Artificial Intelligence*, 20, 197–218.

Anderson is currently working with O'Reilly to combine ACT-R & Leabra in an architecture called SAL (Synthesis of ACT-R and Leabra). "The SAL cognitive architecture is a synthesis of two well-established constituents: ACT-R, a hybrid symbolic-subsymbolic cognitive architecture, and Leabra, a neural architecture".

Key Researchers

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Chapter 5

Adaptive Interfaces

This section includes twenty papers broadly covering adaptive interfaces and automation. Many are concerned solely with adaptive automation, though it is important to point out that the terms are not interchangeable: adaptive interfaces is broader and includes techniques such as modifying the display, input devices, and cuing systems. Using neuroergonomic data to drive adaptive interfaces is a relatively new area, with the first successful systems dating to the early 1990s. While certainly not comprehensive, the following list is intended to provide a representative sampling of the theory, techniques, and application of adaptive interface principles. In general, this work has demonstrated the potential for improvements in performance, but further application has been held back by the need for inexpensive, reliable noninvasive sensors, analysis techniques robust across tasks and days, and adaptation techniques that are consistently effective and well-suited to various tasks.

1. **Berka, C., Levendowski, D. J., Cvetinovic, M. M., Petrovic, M. M., Davis, G., Lumicao, M. N., et al. (2004). Real-time analysis of EEG indexes of alertness, cognition, and memory acquired with a wireless EEG headset. *International Journal of Human-Computer Interaction* , 17 (2), 151-170.**

This paper describes experiments conducted with a wireless EEG headset that is a commercial product being marketed by the company employing the first 7 listed authors. Three studies are presented, including a Warship Commander Task, a visual N-back, and a recognition memory paradigm. The authors conclude that EEG assessed by their system varies reliably with changes in workload.

2. **Byrne, E. A., & Parasuraman, R. (1996). Psychophysiology and adaptive automation. *Biological Psychology* , 42, 249-268.**

This is a review paper that discusses two applications for psychophysiological measurement: developmental testing, and real-time input for adaptive automation. Theoretical background and criteria for candidate psychophysiological measures are also addressed.

3. **de Greef, T., van Dongen, K., Grootjen, M., & Lindenberg, J. (2007). Augmenting cognition: reviewing the symbiotic relation between man and machine. In D. S. Schmorrow, *Foundations of Augmented Cognition*, 439-448. Heidelberg: Springer Berlin.**

This is a theoretically-oriented article discussing adaptive mitigation strategies. The authors argue that mitigation strategies should vary depending on performance, task information, and physiological monitoring data. A cognitive engineering framework for designing adaptive systems is then presented.

4. **Fairclough, S. H., & Venables, L. (2004). Effects of task demand and time-on-task on psychophysiological candidates for biocybernetic control. *Proceedings of the Human Factors and Ergonomics Society 48th Annual Meeting*.**

This proceedings paper evaluated EEG, EOG, and ECG measures of workload with the MATB task and repeated runs over time. The authors conclude that EEG theta and alpha, blink duration, and heart rate/heart rate variability are reliable measures of workload in this complex multitask.

5. **Farrell, S., & Lewanowsky, S. (2000). A connectionist model of complacency and adaptive recovery under automation. *Journal of Experimental Psychology: Learning, Memory, and Cognition* , 26 (2), 395-410.**

The authors propose that automation complacency and recovery from complacency in an adaptive (alternating manual/automated) system can be explained via procedural learning and response biases; they present a connectionist (neural network) model that accounts for several such effects in the MATB task.

6. **Fuchs, S., Berka, C., Levendowski, D., & Juhnke, J. (2006). Physiological sensors cannot effectively drive mitigation alone. In D. D. Schmorrow, K. M. Stanney, & L. M. Reeves (Eds.), *Foundations of Augmented Cognition, 2nd ed.*, 193-200. Arlington, Virginia: Strategic Analysis Inc.**

This is a lessons-learned proceedings paper from the AugCog program which argues that closed-loop adaptive aiding systems need large amounts of information in order to determine the appropriate sort of mitigation to deploy when task overload is detected. Task state, prioritization, and environmental parameters are required to most effectively mitigate overload.

7. **Kaber, D. B., Perry, C. M., Segall, N., & Sheik-Nainar, M. A. (2007). Workload state classification with automation during simulated air traffic control. *The International Journal of Aviation Psychology* , 17 (4), 371-390.**

This paper tested several measures of workload under varying automation conditions in a simulated air traffic control task. Heart rate variability was a poor predictor of workload, while heart rate was somewhat correlated. The authors conclude that performance in a secondary task and subjectively assessed workload were more reliable indicators than cardiac measures in this task.

8. **Kaber, D. B., Prinzel III, L. J., Wright, M. C., & Clamann, M. P. (2002). *Workload-matched adaptive automation support of air traffic controller information processing stages*. (TR: NASA/TP-2002-211032). Langley Research Center, Hampton, Virginia: National Aeronautics and Space Administration.**

This report summarizes adaptive automation work to date and reports on the effectiveness of adaptive automation applied to stages of information processing, from perception to decision making to response implementation. The authors found that the adaptive automation was most effective when applied to lower-level (perception and action) tasks rather than higher-level analysis and decision making. An interesting possible explanation is that the lower-level automation made the fewest assumptions about how participants performed the task, and thus conformed best to their natural methods for performing the task.

9. **Mikulka, P. J., Scerbo, M. W., & Freeman, F. G. (2002). Effects of a biocybernetic system on vigilance performance. *Human Factors* , 44 (4), 654-664.**

This paper implements and tests a vigilance monitoring system based on real-time EEG. Participants performed a standard vigilance task while the rate of the task varied with their EEG-derived engagement index. Performance was improved when the signal rate increased with decreasing engagement.

10. Parasuraman, R., & Wickens, C. D. (2008). Humans: still vital after all these years of automation. *Human Factors* , 50 (3), 511-520.

This is a review paper that examines the levels-of-automation framework, automation reliance, and adaptive automation. The authors suggest that effective implementation of adaptive automation may require flexible reallocation of tasks, though additional research is required to determine conditions for human and system-initiated reallocation.

11. Parasuraman, R., Cosenzo, K. A., & De Visser, E. (2009). Adaptive automation for human supervision of multiple uninhabited vehicles: effects on change detection, situation awareness, and mental workload. *Military Psychology* , 21 (2), 270-297.

The authors report an experiment that required operators to simultaneously operate and/or monitor unmanned vehicles in the air and on the ground. Adaptive automation was implemented via a probe change detection assessment that activated an automated target recognition system. The adaptive aiding condition produced lower subjective workload and higher change detection performance overall, relative to the always-on condition. Individual variability was also noted, with the highest performers showing no particular benefit of the adaptive system.

12. Parasuraman, R., Sheridan, T. B., & Wickens, C. D. (2000). A model for types and levels of human interaction with automation. *IEEE Transactions on Systems, Man, and Cybernetics—Part A: Systems and Humans* , 30 (3), 286-297.

This theoretical paper presents a simple model with four stages in human-system interaction and ten levels of automation. A process for applying this model to system design is then presented with examples. The model is intended to supply an objective means for categorizing and defining appropriate automation as well as evaluation criteria.

13. Prinzel III, L. J., Freeman, F. G., Scerbo, M. W., Mikulka, P. J., & Pope, A. T. (2003). Effects of a psychophysiological system for adaptive automation on performance, workload, and the event-related potential P300 component. *Human Factors* , 45 (4), 601-613.

This paper tested an EEG-based adaptive aiding system with the MATB task. The tracking task was switched from automatic to manual based on the engagement index, while ERPs were recorded to oddball stimuli. Performance was best in the adaptive, negative feedback condition; this condition also produced significantly increased P300 amplitude. The authors suggest that P300 may be a useful indicator of workload though they note that current multi-trial averaging requirements to extract ERPs may render this impractical in real-time systems.

14. Prinzel III, L. J., Parasuraman, R., Freeman, F. G., Scerbo, M. W., Mikulka, P. J., & Pope, A. T. (2003). Three experiments examining the use of electroencephalogram, event-related potentials, and heart-rate variability for real-time human-centered

adaptive automation design. (TR:NASA/TP-2003-212442). Langley Research Center, Hampton, Virginia: National Aeronautics and Space Administration.

This is a NASA technical report that reports on three studies with an adaptive automation system. The first examined EEG, specifically the engagement index; the second ERPs; and the third heart rate variability. The authors conclude that all three measures are diagnostic of workload and potential candidate measures for physiological adaptive automation; though they note that such measures are still tied to the laboratory environment.

- 15. Rothrock, L., Koubek, R., Fuchs, F., Haas, M., & Salvendy, G. (2002). Review and reappraisal of adaptive interfaces: toward biologically inspired paradigms. *Theoretical Issues in Ergonomic Science* , 3 (1), 47-84.**

This theoretically-oriented paper reviews progress in adaptive interface design. Frameworks, taxonomies, and generalized system design models are presented that provide a process and theory for the design of adaptive systems. The paper closes with a discussion of “biologically inspired paradigms”, specifically reframing complex adaptive systems based on the study of the properties of complex biological systems.

- 16. Scallen, S. F., & Hancock, P. A. (2001). Implementing adaptive function allocation. *International Journal of Aviation Psychology* , 11 (2), 197-221.**

This paper presents an experiment with an aviation-oriented multitasking simulation. Adaptive automation was provided by continuously monitoring performance and task variables, which led to improved performance vs. static conditions. Implications for design theory are then discussed.

- 17. Scerbo, M. W. (1996). Theoretical perspectives on adaptive automation. In R. Parasuraman, & M. Mouloua (Eds.), *Automation and human performance: theory and applications*, 37-63. Mahwah, New Jersey: Lawrence Erlbaum Associates.**

This is a review chapter that covers the theoretical bases for adaptive automation as well as research devoted to testing and validating the adaptive paradigm as a means of automation design. Various frameworks are reviewed, along with methods of activation and associated costs and benefits.

- 18. Sheridan, T. B., & Parasuraman, R. (2006). Human-Automation Interaction. In R. S. Nickerson, *Reviews of Human Factors and Ergonomics*, 89-129. Santa Monica: Human Factors and Ergonomics Society.**

This wide-ranging review chapter covers a variety of topics relating to adaptive automation. Trust, etiquette, and quantitative approaches are discussed with representative examples. Various pitfalls are also addressed, including social, political, and ethical considerations.

- 19. Van Orden, K. F., Limbert, W., Makeig, S., & Jung, T.-P. (2001). Eye activity correlates of workload during a visuospatial memory task. *Human Factors* , 43 (1), 111-121.**

This paper reports an experiment designed to test the possibility of using eye tracking measures as input for an adaptive aiding system. Several measures were found to vary

significantly with task difficulty, including blink frequency and duration, saccade extent, and fixation duration. The authors also used these measures as input for an artificial neural network that predicted task difficulty with mean $R=.74$.

- 20. Wilson, G. F. & Russell, C. A. (2003), Real-Time Assessment of Mental Workload Using Psychophysiological measures and artificial neural networks. *Human Factors*, 45, 635-643.**

This paper reports the results of a study utilizing psychophysiological measures as input into a workload classification system. The authors detail the theoretical basis and implementation of this system, and demonstrate accuracy in the MATB task. Adaptive aiding is suggested as the logical application of this real-time workload estimation system.

- 21. Wilson, G. F. & Russell, C. A. (2007). Performance enhancement in an uninhabited air vehicle task using psychophysiological determined adaptive aiding. *Human Factors*, 49, 1005-1018.**

The authors present a logical continuation of the previous paper, by demonstrating that their workload estimation system can be integrated into a highly successful adaptive aiding system, in the context of a uninhabited air vehicle task.

- 22. Wu, C., Liu, Y., & Quinn-Walsh, C. M. (2008). Queuing network modeling of a real-time psychophysiological index of mental workload - P300 in event-related potential (ERP). *IEEE Transactions on Systems, Man, and Cybernetics—Part A: Systems and Humans*, 38 (5), 1068-1084.**

The authors present the results of applying a queuing-network model in order to predict P300 amplitude and latency under varying workload conditions. Analogous brain areas for modules in the model are identified. The authors suggest that this model could be applied for real-time workload prediction as part of an adaptive aiding system.

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Chapter 6

Adaptive Training

While research in the area of adaptive training dates back to the late 1960s, the majority of research conducted and systems developed have focused on performance-based systems, rather than systems capable of continuous assessment as would be possible with neuroergonomic monitoring. This previous work shows that the overall goal has stayed relatively constant: reduce training time and cost; consistently measure performance (those value-added outputs) of the trainee; and provide transfer of training to actual operations. Those adaptive training systems and models documented have focused on the operator's/trainee's previous knowledge, skill, abilities (KSAs), mental load, and task performance to make positive impacts on the trainee's learning experience. Various adaptation strategies in such systems have been documented, but a further investigation of their advantages and disadvantages is necessary. The research and theoretical articles reviewed have suggested that beneficial impacts to trainee performance can be generated in real-time with the aid of psychophysiological measures, and that altering training difficulty and schedule may be the most promising adaptations to focus on with such a system. Future directions for research and development should include work centered on teams of individuals in varying demanding, relevant training situations where systems adapt and provide feedback in real-time.

1. **Coyne, J. T., Baldwin, C., Cole, A., Sibley, C., & Roberts, D. M. (2009). Applying real time physiological measures of cognitive load to improve training. Foundations of Augmented Cognition. *Neuroergonomics and Operational Neuroscience*, 469-478.**

This article presents relevant research in the areas of real time physiological assessment and cognitive load theory, and explains how they can form a basis for adaptive training systems. Rationale for the model of adaptive training based on Wickens' Multiple Resource Theory and Sweller's Cognitive Load Theory are also presented. The authors present that the transition monitoring of novice to expert should be key in such adaptive training approaches.

2. **Dickson, B., & Belyavin, A. (2007). The use of electrophysiological markers of expertise to configure adaptive training systems. In Schmorrow, D., Nicholson, D., Drexler, J., Reeves, L. (eds.) *Foundations of Augmented Cognition*, 4th ed. 138-144. Strategic Analysis, Inc. and the Augmented Cognition International Society, Arlington.**

In this paper, the authors suggest that cognitive workload and expertise level are the driving aspects in adaptive training environments. Methods, analysis and results are presented for their five described training tasks, where electroencephalography (EEG) was recorded throughout all tasks. They discuss that while physiological objective markers (i.e. EEG) of expertise were difficult to determine across tasks, robust relationships were shown for subjects between individual tasks and task-specific expertise.

3. **Vogel-Walcutt, J. J., Nicholson, D., & Bowers, C. (2009). Translating learning theories into physiological hypotheses. Foundations of Augmented Cognition. *Neuroergonomics and Operational Neuroscience*, 678-686.**

This article investigates the use of neuro-physiological hypotheses to optimize the learner's state. Considered were the areas of workload, arousal, and boredom. The authors also consider Meyer's multimedia principles for strategies in information presentation and work in interest research to offset learner boredom.

4. **Parasuraman, R., Cosenzo, K. A., & De Visser, E. (2009). Adaptive automation for human supervision of multiple uninhabited vehicles: effects on change detection, situation awareness, and mental workload. *Military Psychology*, 21 (2), 270-297.**

In this paper, authors performed two experiments investigating the effectiveness of automation (i.e. manual, static, and adaptive) in high workload reconnaissance missions including unmanned aerial and ground vehicle tasks, a communication task, and a change detection task. Measured variables were accuracy, reaction time, situational awareness, and over-all workload, all of which varied with the experiments. Results suggest that human operators can benefit from the use of adaptive aiding techniques.

5. **Deeny, S. P., Haufler, A. J., Saffer, M. & Hatfield, B. D. (2009). Electroencephalographic coherence during visuomotor performance: A comparison of cortico-cortical communication in experts and novices. *Journal of Motor Behavior*, 41 (2), 106-116.**

"Electroencephalographic coherence [EC] is felt to be sensitive to the intactness of connection systems within the brain in that it is a measure of the synchronization of electrical activity between two brain regions, ranging from a single synapse between two neurons to larger networks of interconnected cells" (Holschneider, Leuchter, Scremin, Treiman, & Walton, 1998 [Brain Research Bulletin]). This article documents a study on the effectiveness of EC in researching the relations between cortical interactions and skill level variations. Results showed that experts usually demonstrated lower EC versus novices in the given communication and visuomotor skill task.

6. **Janelle, C. M., & Hatfield, B. D. (2008). Visual attention and brain processes that underlie expert performance: Implications for sport and military psychology. *Military Psychology*, 20 (Supplement 1), s39-s69.**

Janelle and Hatfield state that critical characteristics such as preparation and training, decision-making, attitudes, and stress and coping skills in sports are just as important to operators in the military; allowing lessons learned in sports research using eye movement behavior and other psychophysiological measures to be applied in military research. Captured is a review of sport psychophysiology and concluding thoughts on future research in gaze movements, neurofeedback (e.g. EEG), and genetic marker considerations.

7. **Scerbo, M. W., Freeman, F. G., Mikulka, P. J., Parasuraman, R., Di Nocero, F., & Prinzel, L. J. (2001). The efficacy of psychophysiological measures for implementing adaptive technology. (Technical Report: NASA/TP-2001-211018). Langley Research Center, Hampton, Virginia: National Aeronautics and Space Administration.**

This NASA technical report reviews papers in adaptive technologies. Its focus is on four major areas: 1) the development and implementation of adaptive automation; 2) the search for candidate workload metrics; 3) candidate workload measures focused on electroencephalogram (EEG) and event-related potentials (ERPs); and 4) a NASA-developed biocybernetic system synopsis.

8. **Zotov, M., Forsythe, J., Petrukovich, V., & Akhmedova, I. (2009). Physiological-Based assessment of resilience of training to stressful conditions. In Dylan Schmorrow, Ivy V. Estabrooke, Marc Grootjen (Eds.): Foundations of Augmented Cognition. *Neuroergonomics and Operational Neuroscience*, 563-571. Proceedings from 5th International Conference '09, FAC Held as Part of HCI International 2009 San Diego, CA, USA. Lecture Notes in Computer Science 5638 Springer 2009, ISBN 978-3-642-02811-3.**

In the effort to detect real-time changes in operator workload, the authors use a new method for heart-rate variability (HRV) called CS-index. This index is the ratio of average cardio-intervals and standard cardio-intervals over time. Results indicate that the CS-index is sensitive to task load factors (i.e. task difficulty levels and stress conditions) and can also show differences between experienced and novice operators in simulated conditions.

9. **Wulfeck, W. H. (2009). Adapting Instruction. 687-695. In Dylan Schmorrow, Ivy V. Estabrooke, Marc Grootjen (Eds.): Foundations of augmented cognition. *Neuroergonomics and Operational Neuroscience*, Proceedings from 5th International Conference '09, FAC Held as Part of HCI International 2009 San Diego, CA, USA. Lecture Notes in Computer Science 5638 Springer 2009, ISBN 978-3-642-02811-3.**

The author points out that when adaptive instruction models are created certain variables need to be considered. The basis of adaptation must lie on individual preferences, progress reports, traits/aptitudes, and prior knowledge. One should also consider the instructional actions in the adapting system to include rate and pacing, difficulty, sequencing, method of instruction and medium. It is noted that the implementation of instructor, learner, machine and opponent strategy controls need not be left out of our adaptive paradigms.

10. **Craven, P. L., Tremoulet, P. D., Barton, J. H., Tourville, S. J., & Dahan-Marks, Y. (2009). Evaluating training with cognitive state sensing technology. In Dylan Schmorrow, Ivy V. Estabrooke, Marc Grootjen (Eds.): Foundations of Augmented Cognition. *Neuroergonomics and Operational Neuroscience*, 585-594. Proceedings from 5th International Conference '09, FAC Held as Part of HCI International 2009 San Diego, CA, USA., Lecture Notes in Computer Science 5638 Springer 2009, ISBN 978-3-642-02811-3.**

This article reports that monitoring mental state during training can hinder distraction and engagement and improve training performance. Training included five various techniques: classroom, video, game-based, computer-based and simulator. Cognitive workload was reported to be low for the classroom and video groups, where it was high for computer-based groups. The SMART system was used to provide operator mental state classification in real-time (i.e. EEG recordings) without interrupting performance.

- 11. Sciarini, L. W. & Nicholson, D. (2009). Assessing cognitive state with multiple physiological measures: A modular approach. 533-542. In Dylan Schmorrow, Ivy V. Estabrooke, Marc Grootjen (Eds.): Foundations of Augmented Cognition. *Neuroergonomics and Operational Neuroscience*, Proceedings of 5th International Conference '09, FAC Held as Part of HCI International 2009 San Diego, CA, USA. Lecture Notes in Computer Science 5638 Springer 2009, ISBN 978-3-642-02811-3.**

In this article, the authors explore the use of a modular cognitive state gauge, essentially a system consisting of “multiple minimally intrusive physiological sensors” (p. 540) which measures operator workload in real time. This proposed approach to workload monitoring is based on Wicken’s Multiple Resource Theory, while taking into account the needed initial analyses of individual cognitive processes (i.e. visual, auditory, spatial) termed modules. This analysis would be followed by the integration and synchronization of the modules to measure workload.

- 12. Pope, A. T. & Prinzel, L. J.. Recreation embedded state tuning for optimal readiness and effectiveness (RESTORE). (MS-152, D-318). Hampton, VA; NASA Langley Research Center.**

This paper provides information on the RESTORE concept, which is a closed loop concept driven from previous NASA efforts (i.e. real-time adaptive automation paradigm, Prinzel et al., 2004; physiological self-regulation training procedure for improved task engagement, Prinzel et al., 2002, etc.). The idea seeks to improve psychophysiological coping responses and behavioral and cognitive performance during long duration space flight. To provide regular, engaging maintenance practice to operators during down times, authors propose the use of a physiological self-regulation training system to improve performance, behaviors, and stress coping responses for space maintenance tasks.

- 13. Schnell, T., Cornwall, R., Walwanis, M., & Grubb, J. (2009). The Quality of Training Effectiveness Assessment (QTEA) tool applied to the Naval aviation training context. 640-649. In Dylan Schmorrow, Ivy V. Estabrooke, Marc Grootjen (Eds.): Foundations of Augmented Cognition. *Neuroergonomics and Operational Neuroscience*, Proceedings of 5th International Conference '09, FAC Held as Part of HCI International 2009 San Diego, CA, USA. Lecture Notes in Computer Science 5638 Springer 2009, ISBN 978-3-642-02811-3.**

The QTEA is a prototype demonstration conceived to enable the trainer to assess a student in real-time and provide feedback and/or mitigation in training through the use of physiological sensors. It is intended to include five bio-sensors for continuous monitoring. Benefits to such a system would include real-time adjustment to scenario intensity, depending upon cognitive workload, and a reduction in training cost and time.

- 14. Fairclough, S. H., Venables, L., & Tattersall, A. (2005). The influence of task demand and learning on the psychophysiological response. *International Journal of Psychophysiology*, 56, 171-184.**

This paper presents findings on mental effort used by novice operators via the Multi-Attribute Task Battery (MATB). Physiological measures included four channels of EEG, ECG,

EOG, and respiration rate to measure task demand and learning. Results from respiration rate and EOG support the given hypothesis of skill acquisition putting at risk the psychophysiological variable sensitivity to task demand, whereas EEG and ECG did not.

15. Nahlinder, S. (2009). Flight simulator training: Assessing the potential. (Doctoral Dissertation, Linkoping University, 2009) Dissertation Number 1250

The dissertation report reviews selected studies on mental workload and situational awareness where psychophysiological metrics are used. The author concludes that learning under high workload conditions is not conducive to the learner and their goals. Stated also is the need for psychophysiological data along with individual and instructor ratings to be used in concert for the reliable measurement of mental workload.

16. Wilson, G.F., & Russell, C.A. (2004). Psychophysiological Determined adaptive aiding in a simulated UCAV task. Proceedings of the Second Human Performance, Situation Awareness, and Automation Conference (HPSAA II), Daytona Beach, FL, March 22-25.

This paper discusses an experiment to determine if psychophysiological assessment of operator workload has any impact when adaptive aiding is implemented. Participants monitored UAV operations performing search and destroy tasks. Treatments included no aiding, high-workload aiding, and random aiding. Physiological measures included EEG, ECG, and EOG. Results showed that the artificial neural nets (ANNs) used were able to classify high and low task difficulty at 70% accuracy.

17. Cannon-Bowers, J. A. (Ed); Salas, E. (Ed). (1998). Making decisions under stress: implications for individual and team training. American Psychological Association. Washington, DC, U.S.

Editors and contributing authors describe theories, research, and lessons learned under the Tactical Decision Making Under Stress Program concentrated on complex teaming environments and their performance within. A major focus of the book is the balance between team stresses in complex environments and critical decision-making while training these teams to deal with the coming challenges. It is written to glean insight for military and non-military team operations.

18. Trejo, L. J., Mullane, M., & Stewart, J. (1995) Event-related potentials and electroencephalograms in adaptive operator training: Rationale and annotated bibliography. NPRDC-TN-95-3. Navy Personnel Research and Development Center, San Diego, California.

This report summarizes previous research in the areas of learning, memory, task performance, attention and mental workload with a focus on event-related potentials (ERPs) and electroencephalogram (EEG). One of the main objectives of this report was to see whether “changes in cognitive variables that occur during learning are also reflected in components of task-relevant ERPs and in EEG spectra.”

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Chapter 7

Neuroergonomics and Team Performance

Although technological improvements make it possible to observe the brain at work, few studies have focused on assessing cognitive state and processing across members of a team. As such, research in this area is still quite nascent and opportunities exist for interested scientists to make substantial contributions to the research literature. The articles presented in the following review reveal two general psychophysiological approaches to team research: 1) similarity or synchronicity of autonomic or cortical activity across team members, and 2) neurological bases of joint or coordinated action. These approaches are consistent with the literature on team cognition and performance (e.g., shared mental representations) and may serve to improve our understanding of the dynamic nature of team behavior and performance.

It is worth noting that the scientific terminology in this area has not yet been fully agreed upon or standardized. As such, researchers have used several different terms for similar phenomena, but chiefly the terms *psychophysiological compliance* (e.g., Henning, Armstead, & Ferris, 2009) and *synchronicity* (e.g., Lindenberger, Li, Gruber, & Muller, 2009), along with variations on both, have been utilized to describe a statistical similarity in the autonomic, cortical, or behavioral activity of two or more members of a team engaged in a coordinated task. Where appropriate, the term *psychophysiological compliance* has been employed by the authors of this review to facilitate domain comprehension, with full acknowledgement that the manuscripts described may not utilize that nomenclature.

- 1. Astolfi, L., Toppi, J., De Vico Fallani, F., Vecchiato, G., Salinari, S., Mattia, D., Cincotti, F., & Babiloni, F. (2010). Neuroelectrical hyperscanning measures simultaneous brain activity in humans. *Brain Topography*, 23, 243-256. doi:10.1007/s10548-010-0147-9**

The authors explore a methodology for studying concurrent and simultaneous brain processes during cooperation between individuals using EEG methodologies. In their study, the authors recorded four participants simultaneously while they played a competitive card game (tressette). The authors also describe a method for extending Granger causality to the case of multi-subject analysis, which they argue is necessary to analyze EEG hyperscanning data (i.e., physiological data collected simultaneously from multiple individuals engaged in an interactive task). The experimental results indicated that functional connectivities exist between signals estimated from the ROIs modeling the anterior cingulate cortex (ACC) and the prefrontal cortex (Brodmann Area 8) with the signals estimated in all other modeled cortical areas. The authors further suggest that Granger-sense causal relations between the EEG activity estimated in the prefrontal areas 8 and 9/46 of one player are related to EEG activity estimated in the ACC of their teammate.

- 2. De Bruijn, E.R.A., Miedl, S.F., & Bekkering, H. (2008). Fast responders have blinders on: ERP correlates of response inhibition in competition. *Cortex*, 44, 580-586. doi:10.1016/j.cortex.2007.09.003**

In situations where dyads must perform separate tasks, it may be disadvantageous for the members to attend to and anticipate the other's actions. The authors investigate whether shared representations of actions between co-actors occur during competitive trials or just during coordinated trials. Specifically, the authors tested whether response inhibition is affected by explicit knowledge of another's task during a competitive go/no-go task. Both behavioral and P300 ERP effects were observed in the slow responding and thus unsuccessful competitors. The results suggest that people can differ in the extent to which they incorporate the action plans of others into their own, and that this may be related to successful performance in competitive activities.

- 3. Dixon, K.R., Hagemann, K., Basilico, J., Forsythe, C., Rothe, S., Schrauf, M., & Kincses, W.E. (2009). Improved team performance using EEG- and context-based cognitive-state classifications for a vehicle crew. *Lecture Notes in Computer Science*, 5638, 365-372. doi:10.1007/978-3-642-02812-0_43**

The authors examined an adaptive automation aid as a workload reliever. The experimental task involved two participants, a driver and a gunner, who were asked to drive a prescribed course and fire on simulated enemy targets as they appeared. Both participants were required to complete a secondary callsign communication task while performing their primary tasks (driving and shooting, respectively). The adaptive automation aid utilized two sources of information to determine when to activate. The first was from near-real-time classification of EEG data simultaneously collected from the driver and gunner. The second source was from data derived from the automobile, which was used to infer the ongoing driving context. When activated, the adaptive automation diverted incoming communication task messages from an overloaded participant to their partner (e.g., from the driver to the gunner when the driver was engaged in difficult road maneuvers). When both participants were overloaded, the automated system held incoming messages in a temporary buffer. The authors' results showed improved crew performance on the secondary task and no change in performance of the primary tasks in the adaptive automation condition, supporting the use of physiologically activated adaptive aiding for team task allocation.

- 4. Dumas, G., Nadel, J., Soussignan, R., Martinerie, J., & Garnero, L. (2010). Inter-brain synchronization during social interaction. *PLoS ONE*, 5, 1-10. doi:10.1371/journal.pone.0012166**

The authors were exploring the extent to which oscillatory synchronization in EEG could emerge between two individuals during social interaction. Eighteen participants were paired as 9 dyads and recorded with dual-video and dual-EEG systems. Participants were asked to engage in a game of spontaneous imitation of hand movements (i.e., participants mimicked the hand movements of their partners). The authors assessed the interactional synchrony and turn-taking behavior of the dyads. Nonlinear analysis of the EEG data suggested states of interactional synchrony were correlated with the emergence of an inter-brain synchronization in the alpha-mu band between the right centroparietal regions. In addition, neural synchronization was asymmetrical in the higher EEG frequency bands, which the authors suggest reflects top-down modulation of the roles of model and imitator in the task.

5. Eischeid, T.M., Scerbo, M.W., & Freeman, F.G. (1998). The effects of task partitioning and computer skill on engagement and performance with an adaptive, biocybernetic system. *Proceedings of the Human Factors and Ergonomics Society*, 42, 133-137.

The authors examined the effects of computer skill and task partitioning on a tracking task using an adaptive automation system. The tracking task was partitioned into horizontal and vertical axes, and the adaptive system allocated control of the axes between the human and the system in real time. Task allocation was determined by participants' near-real-time level of task engagement, indexed using EEG data. Results indicated that sharing the task with an expert skill-level computer yielded performance that was comparable to the participant performing the task manually, while pairing with a novice skill-level computer degraded performance compared to manual performance. Of interest in this experiment is the treatment of the computer system as an approximately equal performance partner, whose role was to monitor and maintain participants' ongoing task engagement.

6. Elkins, A.N., Muth, E.R., Hoover, A.W., Walker, A.D., Carpenter, T.L., & Switzer, F.S. (2009). Physiological compliance and team performance. *Applied Ergonomics*, 40, 997-1003. doi:10.1016/j.apergo.2009.02.002

This study presents a psychophysiological approach to predicting team performance based on previous research showing that physiological compliance reveals the rapport or cohesion among group members. Heart rate variability was examined across teams of four during a military room clearing task. Results suggest a relationship between team performance and physiological compliance in teams, with high performing teams showing higher physiological compliance than low performing teams. The authors suggest that physiological compliance may be useful in assessing team training and team cohesion.

7. Espevik, R., Helge Johnsen, B., Eid, J., & Thayer, J.F. (2006). Shared mental models and operational effectiveness: Effects on performance and team processes in submarine attack teams, *Military Psychology*, 18 (Suppl.), S23-S36. doi:10.1207/s15327876mp1803s_3

The effect of team familiarity on performance and stress/arousal was observed in a submarine attack crew simulation. The purpose of the study was to examine the effects of shared mental models on team performance. The authors hypothesized that teams who had trained together would develop compatible shared mental models which would lead them to better task performance and less cardiovascular reactivity (as an index of stress) compared to teams with the same degree of training, but who had not practiced the task with their teammates prior to experimental task performance. The authors found that teams who had trained together successfully hit more targets and showed qualitative and quantitative changes in the amount and types of information exchanges they engaged in. Teams who trained together also showed less physiological arousal. The authors attributed these differences to the effects of compatible shared mental models formed during team interactions and training on team performance.

8. Gil, M.C., & Henning, R.A. (2000). Determinants of perceived teamwork: Examination of team performance and social psychophysiology. *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, 44, 743-746.

The authors investigated the effects of perceived teamwork and team psychophysiology on team performance in a two-person continuous tracking task. Two-person teams performed a computer-based, simulated teleoperation task. Their authors' results suggest that team performance and some social psychophysiological measures (IBI cross-correlation) were indicative of perceived teamwork.

9. Henning, R.A., Armstead, A.G., & Ferris, J.K. (2009). Social psychophysiological compliance in a four-person research team. *Applied Ergonomics*, 40, 1004-1010. doi:10.1016/j.apergo.2009.04.009

The authors examined a measure of social psychophysiological compliance (SPC) based on heart rate variability as a predictor of teamwork effectiveness as rated by members of a four person team. Speech and heart rate variability data were collected from participants during 20 one-hour meetings which occurred over a 6-month period. One measure examined, SPC during periods of sequential speech, was particularly effective; it was predictive of team ratings of team productivity, quality of communication, and ability to work together. The authors argue that SPC exhibits some potential as a non-invasive, near-real-time monitor of teamwork effectiveness, but acknowledge that the proposed relationship warrants further investigation and replication before wider acceptance and use.

10. Henning, R.A., Boucsein, W., & Gil, M.C. (2001). Social-physiological compliance as a determinant of team performance, *International Journal of Psychophysiology*, 40, 221-232. doi:10.1016/S0167-8760(00)00190-2

The authors introduce a cybernetic model of behavior that may predict team performance from the correlation of physiological measures between team members, which the authors termed *physiological compliance* (PC). Specifically, the authors examined compliance in electrodermal activity (EDA), heart rate, and breathing in two-person teams performing a continuous tracking task. Visual contact between participants was also manipulated to determine if this would influence team performance or measures of PC. The results of the study indicated that several aspects of team performance were predicted by measures of PC, and that IBI cross correlation was consistently the strongest predictor. Visual contact, on the other hand, did not appear to influence team performance or PC. The authors argue that their results support the utility of PC for assessing teamwork in team tasks.

11. Hwang, S.L., Liang, G.F., Lin, J.T., Yau, Y.J., Yenn, T.C., Hsu, C.C., & Chuang, C.F. (2009). A real-time warning model for teamwork performance and system safety in nuclear power plants. *Safety Science*, 47, 425-435. doi:10.1016/j.ssci.2008.07.011

A new approach for predicting team performance was developed from measures of heart rate variability, team response time, and error rates. Participants completed the experiment in teams of three. Their task was to power up a simulated nuclear power plant to normal operating levels.

The results of the experiment indicated a positive correlation between team error rates and the interval of event arrival time. The authors suggest that this indicates a need for a pre-alarm device to help operators who have become less vigilant with time-on-task, and that their proposed warning system could be used to monitor and maintain appropriate operator mental workload.

- 12. Lindenberger, U., Li, S.C., Gruber, W., & Muller, V. (2009). Brains swinging in concert: Cortical phase synchronization while playing guitar. *BMC Neuroscience*, 10, 1471-2202. doi:10.1186/1471-2202-10-22**

In this study, the authors investigated the synchronized cortical (EEG) activity of two guitarists during interpersonally coordinated action (playing a short melody together). In the manuscript, the authors identify several EEG frequency bands suspected to be related to initiating and maintaining interpersonal coordination of action. Their results indicated significant synchronicity during several phases of coordinated activity. The authors argue that the observed synchronicity reflects similarities in the temporal properties of participants' percepts and actions.

- 13. Marshall, S.P. (2009). What the eyes reveal: Measuring the cognitive workload of teams. *Lecture Notes in Computer Science*, 5620, 265-274. doi:10.1007/978-3-642-02809-0_29**

The author describes a method for near-real-time assessment of cognitive workload, the Networked Evaluation System (NES), which uses a network of coordinated eye-trackers to monitor team members working together on a team task. Two experiments utilizing the NES are also described. The first is a military application with teams of officers working together on a simulated joint relief mission, and the second is a fatigue study with teams of individuals working together in a simulated lunar search and recovery mission. In both studies, the NES system provided near-real-time assessment of team members' mental workload as they performed their tasks. The author suggests that the NES system could be useful for alerting team members or a supervisor when levels of workload are unacceptably high or low.

- 14. Montague, P.R., Berns, G.S., Cohen, J.D., McClure, S.M., Pagnoni, G., Dhamala, M., Wiest, M.C., Karpov, I., King, R.D., Apple, N., & Fisher, R.E. (2002). Hyperscanning: Simultaneous fMRI during linked social interactions. *NeuroImage*, 16, 1159-1164. doi:10.1006/nimg.2002.1150**

The authors describe a new methodology for conducting experiments using linked fMRI units to simultaneously record two participants engaged in social interaction, which the authors term *hyperscanning*. Data supporting the technique is presented from a study of two participants engaged in a simple deception task. Several potential approaches and applications for hyperscanning are described.

- 15. Murai, K., Okazaki, T., & Hayashi, Y. (2004, April). *Measurement for mental workload of bridge team on leaving/entering port*. Paper presented at the 2004 Position Location**

and Navigation Symposium (PLANS), Monterey, CA. Retrieved from
<http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=1309069>

In this experiment, the authors assessed the mental workload of three bridge crews using heart rate variability. The authors monitored the bridge crews as they were entering or leaving a port, as this is a difficult and demanding period during ship operations. The results of the experiment support the utility of heart rate variability for near-real-time monitoring of mental workload in complex, real-world team tasks.

- 16. Newman-Norlund, R.D., Noordzij, M.L., Meulenbroek, R.G.J., & Bekkering, H. (2007). Exploring the brain basis of joint action: Co-ordination of actions, goals and intentions. *Social Neuroscience*, 2, 48-65. doi:10.1080/17470910701224623**

In this manuscript, the authors provide a review of the findings in cognitive neuroscience related to the coordination of actions, goals, and intentions of cooperating humans, with the goal of articulating the functional network upon which joint action is hypothesized to be dependent. While not directly targeted to neuroergonomics, this review is an excellent starting point for understanding the hypothesized brain systems underlying interpersonal coordination, imitation, and action.

- 17. Oullier, O., de Guzman, G.C., Jantzen, K.J., Lagarde, J., & Kelso, J.A.S. (2008). Social coordination dynamics: Measuring human bonding. *Social Neuroscience*, 3, 178-192. doi:10.1080/17470910701563392**

In this experiment, the authors explored the phenomenon of spontaneous social coordination, which occurs when humans self-synchronize aspects of their behavior while interacting (with the world, each other, etc.). The authors hypothesized that spontaneous synchrony could develop between humans as a result of information exchange. Pairs of participants were asked to perform a finger movement task by themselves, in the presence of their partner, and by themselves again. The results of the experiment revealed that spontaneous phase synchrony (i.e., coordinated finger wagging) emerged as soon as participants could observe the actions of their partner, even without explicit instruction to coordinate with each other. Though not addressed in the manuscript, the results of the experiment suggest that some degree of psychophysiological compliance may occur naturally between teammates as a result of their social interactions.

- 18. Sebanz, N., Rebbechi, D., Knoblich, G., Prinz, W., & Frith, C.D. (2007). Is it really my turn? An event-related fMRI study of task sharing. *Social Neuroscience*, 2, 81-95. doi:10.1080/17470910701237989**

In this study, the authors used event-related fMRI to identify neural correlates of task-sharing in pairs. Their results indicated that even when coordination is not required, processing of a co-actor's task occurs, providing a potential measure of team coordination. The authors suggest that activation differences in the ventral medial frontal cortex and the anterior cingulate cortex may indicate changes in stimulus processing during coordinated performance.

- 19. Stevens, R., Galloway, T., Berka, C., & Behneman, A. (2010, March). *Identification and application of neurophysiologic synchronies for studying the dynamics of teamwork.* Paper presented at the 19th Behavior Representation in Modeling & Simulation (BRIMS) Conference, Charleston, SC. Retrieved from <http://brimsconference.org/archives/2010/papers/10-BRIMS-103%20Stevens.pdf>**

The authors describe a process for collecting and combining EEG signals derived from individual members into a normalized expression of those signals for the team as a whole. The authors illustrate the utility and limitations of their measure in three experiments, including a team emotion recall research study, an educational study where teams of high school students solved substance abuse simulations, and a complex training study where Submarine Officer Advanced Candidate trainees performed submarine piloting and navigation exercises.

- 20. Stevens, R., Galloway, T., Berka, C., & Sprang, M. (2009) Can neurophysiologic synchronies provide a platform for adapting team performance? *Lecture Notes in Computer Science*, 5638, 658-667. doi:10.1007/978-3-642-02812-0_75**

EEG measures of workload and engagement were assessed across members of a team performing a substance abuse management simulation. Neurophysiologic synchrony within the team reflected the team's efficiency. The approach presented may serve as a means to monitor team performance in real world problem-solving tasks.

- 21. Tognoli, E., Lagarde, J., De Guzman, G.C., & Kelso, J.A.S. (2007). The phi complex as a neuromarker of human social coordination. *Proceedings of the National Academy of Sciences of the United States of America*, 104, 8190-8195. doi:10.1073/pnas.0611453104**

This article identifies potential markers for the neurological observation of movement coordination between partners. The authors used a dual-EEG system to identify neural signatures of effective, real-time coordination between dyads performing a finger movement task. The mu rhythm was identified as a potential marker of somatosensory awareness and the phi rhythm may serve as a marker of spontaneous coupling of behavior between individuals. The authors also identify and discuss the likely brain regions related to each rhythm.

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Acronym List

5-HTT	Serotonin transporter protein
A2M	Alpha-2-macroglobulin
ACC	Anterior cingulate cortex
ACFSO	Age at CFS onset
ACTN3	Alpha-actinin-3
ACT-R	Adaptive Control of Thought--Rational
AD	Alzheimer's disease
AFRL	Air Force Research Laboratory
ANNs	Artificial neural nets
APOE	Apolipoprotein E
Arg	Arginine
Arg16Gly	Beta(2)-adrenergic receptor
ASIC3	Acid sensing ion channel
AugCog	Augmented cognition
AVPR1a	Arginine vasopressin 1a receptor
BDNF	Brain-derived neurotrophic factor
BOINC	An open-source software platform for computing using volunteered resources
BOLD	Blood oxygen level dependent
bp	base pairs
CAMTA1	Calmodulin-binding transcription activator 1
CBG	Corticosteroid-binding globulin
CD-1	Cluster of differentiation 1
CFH	Complement factor-H
CFS	Chronic fatigue syndrome

CHRNA4	Cholinergic Receptor for Nicotine Alpha 4
CK	Creatine kinase
CK-B	Creatine kinase, brain type
CK-M	Creatine kinase, muscle type
COL9A2	Collagen alpha-2(IX) chain gene
COMT	Catechol-O-methyltransferase
CPT	Cold pressor test
CSF	Cerebrospinal fluid
D1, D2, D3	Dopamine receptor genes
DDR&E	Director of Defense Research and Engineering
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DNA	Deoxyribonucleic acid
DoD	Department of Defense
DTNBP1	dystrobrevin binding protein 1
EAD	Early stage-Alzheimers disease
EC	Electroencephalographic coherence
ECG	Electrocardiography
EDA	Electrodermal activity
EEG	Electroencephalography
ENO1	A-enolase
EOG	Electrooculography
EPIC	Executive Process-Interactive Control
ERBB4	Gene that codes for a cell surface receptor in the epidermal growth factor family
ERPs	Event related potentials

FASTKD2	FAST kinase domains 2, gene that codes for a mitochondrial protein
fMRI	functional magnetic resonance imaging
Glo1	Glyoxalase
GLUL	Glutamine synthetase
Gly	Glycine
GWAS	Genome-wide association scan/study
GWI	Gulf War Illness
HERITAGE	a three-phase study (1992-2004) researching genetics and exercise
HG	Gandgrip
HLA	Guman leukocyte antigen
HLA-DRB1	Gene for beta chain of the HLA
HPC	High performance computing
HR	Heart rate
HRV	Heart rate variability
IBI	Inter-beat interval
IKZF2	Gene that encodes the zinc finger protein Helios
IL10	Interleukin-10, an IS gene
IPL	Inferior parietal lobule
IQ	Intelligence quotient
IS	Immune system
KIBRA	Kidney and brain protein
KSAs	Knowledge, skills, and abilities
LOD	Logarithm (base 10) of odds; a representation of the likelihood of a linkage between two genetic traits
LTM	Long term memory

MAP	Mean arterial pressure
MAP2	Microtubule associated protein 2
MATB	Multi-attribute task battery
MCI	Mild cognitive impairment
MED	Multiple epiphyseal dysplasia
MRI/MRS	Magnetic resonance imaging/spectroscopy
MS	Mental stress
mI	myo-inositol ratio
mRNA	messenger ribonucleic acid
N1	a negative event-related potential usually peaking at 80-120 milliseconds post stimulus in adults
N2	a negative event-related potential component that peaks 200-350 milliseconds post stimulus in adults, following N1
NAA	N-acetylaspartate
NASA	National Aeronautics and Space Administration
NES	Networked Evaluation System
NMR	Nuclear magnetic resonance spectroscopy
NOS1	Neuronal nitric oxide synthase 1
NRXN1	Neurexin 1
P2X4	Purinergic type 2x receptors
P2X5	Purinergic type 2x receptors
P3(00)	a positive event related potential that peaks 300 or more millisecond post stimulus, elicited by infrequent, task-relevant stimuli
PAI-1	Plasiminogen activator inhibitor type 1
PALM	Performance and Learning Models
PARD3B	Partitioning defective 3 homolog B gene

PC	Physiological compliance
PCr	Phosphocreatine
PDP	Parallel distributed processing
PIN1	Peptidyl-prolyl cis/trans isomerase 1
PKM2	Pyruvate kinase M2
PTMs	Post-translational modifications
PTSD	Post-traumatic stress disorder
QTEA	Quality of training effectiveness assessment
QT (L)	Quantitative trait (locus)
RAGE	Receptor for advanced glycation end product
RefSeq	Reference sequence
RESTORE	Recreation embedded state tuning for optimal readiness and effectiveness
RF	Radio frequency
RNS	Reactive nitrogen species
SAH	Subarachnoid haemorrhage
SAL	Synthesis of ACT-R and Leabra
SERPINA6	Gene coding for corticosteroid-binding globulin
SMART	Sensor-based mental assessment in real-time system
SNPs	Single nucleotide polymorphisms
SOAR	Symbolic cognitive architecture
SPAG16	Gene for sperm-associated antigen 16
SPC	Social psychophysiological compliance
STM	Short term memory
TAAR6	Trace-amine associated receptor 6 protein
TLR4	Toll-like receptor 4, an IS gene

TRPV1	Transient receptor potential vanilloid type 1
VCI	Vascular cognitive impairment
WAIS-R	Wechsler Adult Intelligence Scale-Revised